HANDBOOK OF MATERIA MEDICA, TOXICOLOGY, AND PHARMACOLOGY

HANDBOOK OF MATERIA MEDICA, TOXICOLOGY, AND PHARMACOLOGY

FOR STUDENTS AND PRACTITIONERS OF MEDICINE

BY

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FOURTH EDITION

With 35 Illustrations, Including 4 in Color

ST. LOUIS
THE C. V. MOSBY COMPANY
1949

Third Edition Reprinted
July, 1944
March, 1945
April, 1946
January, 1947
November, 1947

Printed in the
United States of America

Press of
The C. V. Mosby Company
St. Louis

To
My Wife

GERTRUDE ERMENTROUT DAVISON

This Book Is
Affectionately Dedicated

". . . receiving thankfully all that physiology or chemistry or another science can give us, let us still hold that that alone is true which is proved clinically, and that which is clinically proved needs no further evidence."

—Sir James Paget

"If ever the human race is raised to its highest practicable level intellectually, morally, and physically the science of medicine will perform that service."

—Descartes

"What helps the individual patient most is to be taken as the best treatment, for him, whether it be possible or not to analyze its action in every detail."

—Wenckebach

"It is not to be imagined that he should know the remedies of diseases who knows not their original causes."

—Aurelius Cornelius Celsus

"Let us, a little, permit Nature to take her own way; She better understands her own affairs than we."

—Michel de Montaigne

"The best inspirer of hope is the best physician."

—Samuel T. Coleridge

"A merry heart doeth good like a medicine. . . ."

—Proverbs 17:22

"Books—to judicious compilers, are useful; to particular arts and professions, absolutely necessary; to men of real science they are tools."

—Samuel Johnson

PREFACE TO FOURTH EDITION

The aim of this revision is to present again that information about drugs essential for the student of medicine and the practicing physician; to present sufficient information about the practical use of drugs to assist the student in the transition from his preclinical years to clinical studies.

The trend today is toward a closer correlation between the basic sciences and clinical medicine. If the therapeutic use of drugs is completely dissociated from the other drug information, an unavoidable gap will always exist in the student's knowledge of these important substances.

As in former editions, the essentials of pharmacy are presented in order to prepare the student to administer drugs intelligently. Prescription writing is again given a place of prominence. Intelligent drug therapy is closely associated with the writing of good prescriptions.

The chapter on Toxicology has not been enlarged. The material, however, has been revised and reorganized in order to allow for a brief discussion of industrial toxicology. A knowledge of the fundamental principles underlying the injurious action of substances used in industry is essential to every student of medicine and every practicing physician.

A characteristic of American medicine has been the constant search for new medicines and the development of new uses and methods for older remedies. Significant new remedies are discussed, including polymyxin, aureomycin, antihistamines, folic acid, rutin, BAL, antithyroid drugs, newer antimalarials, "nitrogen mustards," digitoxin, blood fractions, radioactive phosphorus, and many more. New information on hormones and also on vitamins is given.

The revision of this book has aimed at keeping faith with those who have honored me by using my previous editions, by presenting useful, practical, and up-to-date information. The reception accorded the previous editions has been gratifying and has made the preparation of this revision a pleasant task.

I wish to thank many kind readers who have offered valuable suggestions for improving this edition. Finally, it is a pleasure to acknowledge my indebtedness to Gertrude Ermentrout Davison for her encouragement and painstaking editorial assistance.

FORREST RAMON DAVISON.

Minneapolis, Minnesota.

PREFACE TO FIRST EDITION

In the following pages I have attempted to present, as briefly as seems consistent with thoroughness, the information about drugs essential for the student of medicine and the practicing physician.

In writing this book I have kept in mind two guiding principles: First, that pharmacology is an integral part of medicine; obviously, the theoretical study of drugs should not be divorced from the practical application. Second, there should be a judicious limitation of the subject matter consistent with its importance in the field of medicine. I have selected for discussion those commonly used drugs with established effectiveness, eliminating superfluous material.

Although the important newer drugs have not been neglected in this volume, the student of medicine and the physician must remember that these newer pharmaceutical products supplement, but do not necessarily replace, those preparations the composition, action, and therapeutic results of which have been established by continued usage over the years. From the extreme eagerness with which newer untried preparations meet with approval we might believe that the drugs found in the U.S.P., the N.F., and the N.N.R. were of little therapeutic value. It is admitted that all of the large numbers of drugs and preparations included in the U.S.P., N.F., and N.N.R. are not of significant therapeutic value, thus requiring critical selection by the practicing physician. It has been my aim, in so far as possible, to present in this volume those drugs with established therapeutic value.

A classification of drugs which shall answer all purposes has never been, and probably never will be presented. Guided chiefly by the needs of the medical student, I have presented a classification of drugs which should help to simplify, for the student, the rapidly accumulating mass of information concerning drugs found in medical literature. The site of action and the therapeutic activity of the various drugs have been used in the development of the classification presented. Such a systematic classification has proved very effective in teaching and provides the student with a background from which a better understanding of pharmacology can be acquired.

It has been my aim in constructing this volume to present pharmacology as an applied subject. Pharmacology should be taught in the classroom, laboratory, and clinic. Unless the scientific evidence for the pharmacological action of drugs be directly tied up with the clinical application of drugs, the student will derive little practical benefit from his course in pharmacology. Hence I have omitted highly specialized scientific details, beautiful in their intricacy, but of little value to the future physician, and have substituted fundamental and practical applications of drug action.

The role of drugs in the treatment of disease is illustrated by the large number of prescriptions of merit which are included in the text. These not only furnish the student with an armamentarium of drugs for his future use, but also serve as models for prescription writing. It is felt that a fundamental knowledge of the therapeutic uses of drugs, supplemented with the ability to write correct prescriptions, is of value in bridging that gap between the preclinical and clinical years that so frequently exists.

A complete bibliography would be inappropriate for a book of this size, but for the sake of those who wish to do additional reading a limited number of references have been given at the end of each chapter.

Textbooks represent material supplied by thousands of workers, hence, it is impossible to assign credit where credit is due. I have utilized current literature and texts in pharmacology, physiology, biochemistry, and medicine for material used in the preparation of this volume. Where direct reference is possible, this has been made in the text.

While the liberal pursuit of knowledge should never be discouraged, we must face the fact that too often the required time cannot be found in the medical curriculum to make an exhaustive study of each subject; consequently, I have tried to write a text such as I would have been glad to have had as a guide while pursuing my training in pharmacology.

I am deeply grateful to Doctors K. A. Siler, R. Gregory, E. L. Wilbur, and C. H. McDonald for valuable suggestions tending to improve the scope and value of this work. To my wife, I am deeply indebted for her assistance and encouragement in writing this book. Finally I wish to thank The C. V. Mosby Company and Dr. D. E. Jackson, who have kindly permitted the reproduction of many valuable figures.

FORREST RAMON DAVISON.

Little Rock, Arkansas.

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HANDBOOK OF MATERIA MEDICA, TOXICOLOGY, AND PHARMACOLOGY

PART I

CHAPTER I

THE BASIC PRINCIPLES OF PHARMACOLOGY

Definitions

Pharmacology (Gr. *pharmakon,* drug; *logos,* learning or science) is the science of the action of medicines, their nature, preparation, administration, and effects. The following divisions of the field are recognized:

PHARMACODYNAMICS (Gr. *pharmakon; dynamos,* power), the study of the action of drugs on living organisms.

PHARMACOTHERAPEUTICS, the study of applying drugs in disease. *Therapeutics* includes all remedial agents and measures which promote comfort and well-being, and the healing of the patient, i.e., psychotherapy, physiotherapy, dietotherapy, and occupational medica.

Materia Medica (L. *materia,* material; *medica,* medical), that branch which deals with drugs, their sources, preparations, actions, and uses.

Pharmacognosy (Gr. *pharmakon; gnostic,* seeking to know) deals with the origin, anatomical structure, and chemical composition of crude drugs.

PHARMACEUTICAL CHEMISTRY, the study of the chemistry and the chemical preparation of drugs.

PHARMACY, the study of preparing and dispensing drugs for medicinal purposes.

TOXICOLOGY (Gr. *toxikon,* poison; *logos,* understanding), the sum of what is known regarding poisons; the scientific study of poisons, their action, their detection, and the treatment of conditions produced by them.

What Is a Drug? The United States Pure Food and Drug Act defines a *drug* as follows: "The term drug as used in this act shall include all medicines and preparations recognized in the United States Pharmacopoeia or the National Formulary for internal or external use and any substances or mixture of substances intended to be used for the cure, mitigation or prevention of disease of either man or other animals."

Scope of Pharmacology

Pharmacology is one of the more recent developments of the medical and biological sciences. Although closely related to other sciences, it is neither possible nor advisable to set up too sharp a line of demarcation between it and other studies, such as pharmacy, physiology, pathology, biochemistry, and internal medicine.

Recent progress in pharmacology has been largely dependent on the application of the great principles which were laid down by those outstanding pioneers of medicine and surgery—William Harvey and John Hunter. Such pioneers of pharmacology as Arthur Robert Cushny and John Jacob Abel have contributed much to the advancement of this science. Since early times our knowledge of the use of drugs has been obtained as the result of experience and empirical observation. In some instances "fortunate mistakes" have resulted in beneficial effects, not only on the individual patient, but also by suggesting a new method of treatment for fellow sufferers. For example, Trousseau in 1864 intended to prescribe tincture of digitalis for a patient suffering from exophthalmic goiter, but actually wrote down tincture of iodine; the next time he saw the patient, he was astonished at the extraordinary improvement.

Recently in evaluating remedies, the test of experiment has supplemented empirical observation. Every new drug is tested chemically and clinically before it is received into the ranks of established therapeutic remedies. Animal experimentation has played an important part in the modern advances in pharmacology. Animal experiments are also utilized for testing the toxicity and potency of all new drugs. This acts as a means of safeguarding human beings from the dangers of overdosage, and ensures greater dependability and efficiency of action in treatment.

During the present century chemical research has led to the discovery of many new compounds and the pharmacological and physiological actions of many of these substances have been studied. The linkage between the chemical constitution and the pharmacological action has been so closely studied that the pharmacologist can, to some extent, predict the probable therapeutic action of a drug. Such investigations as these led Ehrlich to discover salvarsan, and similar researches on barbituric acid led to the discovery of many valuable barbituric acid compounds, such as pentobarbital, phenobarbital, and others.

The discovery and development of the sulfonamide drugs represent one of the most dramatic achievements in medicine. The advent of penicillin, streptomycin, and other products of microbic origin may prove of even greater importance. It seems of special significance that several classes of reagents are now competing for supremacy as anti-infective agents in conditions which were formerly unresponsive to any type of therapeutic agent. More recently, nuclear physics has provided procedures whereby the metabolism of a drug can be followed by means of so-called isotope-tracer methods.

We must not lose sight of the fact that the great interest of pharmacology does not lie in its purely biological aspects but rather in its relation to the treatment of disease. The physician must have a knowledge of both normal and pathological processes and, with this knowledge at hand, he must attempt to administer that drug which will modify the disorganized process or some other physiological process in order to bring about the desired result in the patient. For example, drugs may be administered to relieve pain, to induce sleep, to reduce inflammation, to contribute to the comfort of the patient, and for numerous other reasons. Thus, drugs are administered to enable nature better to counteract the pathological processes present; to increase or decrease some physiological function in order to alleviate the sufferings of, or to cure, the patient. Hence, knowledge of pharmacology is essential for the practice of medicine.

METHODS OF DRUG ADMINISTRATION

Successful treatment of disease by drugs depends on a thorough knowledge of the various methods of administration, and on the ability to select the most direct channel available to reach the seat of the disease. Therefore, we must decide whether we desire local action, i.e., action at point of application, or general action, i.e., systemic action that occurs after absorption. *The effect and success of a remedy are often determined by the method of administration.*

Regardless of the path of administration of a drug the remedy eventually reaches the circulation. The results vary directly with the rate of absorption. As a *general rule* the rate of the absorption occurs in the following order, beginning with the most rapid:

1. Blood stream (vein)
2. Inhalation
3. Intraperitoneal
4. Intramuscular
5. Subcutaneous (hypodermic)
6. Intradermal
7. Oral
8. Skin (local application)

Drugs are usually administered by one of the following methods:

1. **Oral Administration.**—This method of drug administration is the most convenient and the most common method used. Drugs may be absorbed from any part of the alimentary tract; the rate of absorption varies greatly with the different portions. Drugs are usually so quickly swallowed that little absorption occurs in the mouth. The oral route is the best route for drugs intended for local action on the upper digestive tract. Absorption from the stomach varies with the form of the drug, the solvent, and the amount of food in the stomach. To act directly upon the stomach a drug should be given before meals. Drug absorption is most rapid from the small intestine; here the conditions are very favorable for absorption—an extensive surface, long sojourn, folds, villi, and segmental movements. To insure direct action upon the intestine and to avoid the action of gastric juice, a drug may be given in the form of a pill coated with salol. When, however, the drug deranges digestive functions, causes nausea and vomiting, or produces gastric inflammation or ulceration, or when digestion destroys the remedy, then other routes of administration are indicated.

Drugs taken by mouth generally pass through the portal circulation and through the liver before entering the systemic circulation. The other routes result in more direct absorption into systemic circulation, thus by-passing the liver which may store or destroy all or part of the drug. Consequently oral doses are usually larger than for other routes. Furthermore, drugs given by routes other than by mouth, may produce an increased sensitivity, as no storing or detoxifying action by the liver is present.

2. **Rectal Administration.**—This means of administration is used to obtain both local and general effects, and for exciting evacuation. If a drug cannot be given by mouth, because of nausea and vomiting, or because of a desire to limit peristalsis, it may be administered by rectum, either in the form of enemas and suppositories, or as medicated saline solutions.

The rectum is a good absorbing surface for many drugs. The rectal dose is often the same as, or smaller than, that for oral administration, but no fixed ratio exists between oral and rectal dosages. The remedy is introduced through a rectal tube which is inserted about 10 inches. After the material is injected the rectal tube is slowly removed. Salts and narcotics are absorbed more rapidly

from the rectum than from the oral route. Glucose solutions are often administered by the rectal route. Certain drugs, such as tribromoethanol and ether-in-oil, are regularly given by this route. Drugs administered by rectum may, by retroperistalsis, be carried back as far as the cecum and thus be absorbed by the colon. Rectal administration is unesthetic and is prone to produce proctitis.

Parenteral Administration

Parenteral administration is the administration of drugs under the skin or mucous membrane. The medicinals used should be sterile and free from pyrogens. Parenteral solutions must be given with aseptic precautions.

3. **Subcutaneous Administration.**—Subcutaneous administration is of more recent origin and is widely used. By this method drugs are injected through a fine hollow needle into the subcutaneous tissue. Drugs administered in this manner are promptly absorbed through the lymphatic or blood capillaries into the systemic circulation.

The majority of parenteral injections are given subcutaneously. The tendency to severe and dangerous reactions are much less than with intravenous injections although the chance of infection is somewhat greater. Unless the drug is irritating or must be injected directly into the blood stream to be effective, the subcutaneous route is the one of choice.

Procedure: The skin is sterilized, drawn taut, and the needle (gauge 24 to 26) quickly inserted. It is best to withdraw the plunger slightly after the needle is inserted, and before the injection is made, to make sure the needle has not entered a vein.

Hypodermoclysis (subcutaneous infusion) is the introduction of large amounts of a drug, usually in physiological saline or some other isotonic solution, into subcutaneous tissue.

4. **Intravenous Injection.**—When immediate action is indicated, a drug may be given directly into the blood stream; for instance, the administration of strophanthin in case of acute cardiac dilatation. Doses under 20 cc. may be rightfully considered as *intravenous*, while the term *infusion* is used for larger doses usually administered by a "gravity apparatus." The advantages of this method are:

a. Instant action.
b. More accurate adjustment of dosage.
c. Avoidance of gastrointestinal irritation.
d. Avoidance of subcutaneous and intramuscular irritation, i.e., irritation caused by tartar emetic.

The disadvantages of intravenous injection are:

a. Adverse reactions due to altering of equilibrium of blood colloids.
b. Certain substances incompatible with blood, e.g., acids and metallic salts.
c. Drugs must be in solution.
d. Necessity for surgical technic.

The toxicity of a drug may be greatly reduced by having it well diluted and by injecting it slowly. The intravenous dose is usually smaller than the oral dose. Intravenous injections are usually made into the antecubital veins. *Method:* A tourniquet is applied over the upper third of the arm to produce venous stasis. The needle is then introduced aseptically; the plunger is drawn back and as soon as blood appears the needle is inserted from 0.5 to 1 cm. within the vein, the

tourniquet is loosened, and the solution injected slowly. If a chill follows the injection, the patient should be warmly covered. In severe reactions subcutaneous injection of 0.5 cc. (7 minims) of epinephrine solution may be indicated.

In case the veins of the forearm are not available, the superficial veins of the hand or foot, the femoral vein, or the jugular vein may be used. In infants the jugular vein may be used and in extreme cases the longitudinal sinus of the skull. Accidents are rare with most substances, and there should be no hesitation in using intravenous administration if this route is indicated.

Intravenous infusions are given when immediate need of fluid or nourishment or when the special effects of hypertonic or hypotonic solutions are indicated. Physiological saline, with or without glucose or hypotonic sodium chloride (0.5%) or hypertonic sodium chloride (15%) are often used.

Five hundred cubic centimeters of fluid may be given in from 15 to 30 minutes, or even larger amounts if given by continuous drip over several hours.

5. **Intramuscular Administration.**—In this method, deep injection is made of oily or aqueous solutions of irritant drugs into the skeletal muscles, preferably the deltoid, gluteal, or lumbar muscles. Absorption is prompter than after subcutaneous administration, and there is less liability of abscess formation or necrosis, due to great vascularity. In making an intramuscular injection the needle attached to the syringe should be plunged into the muscle. Before expulsion one should aspirate to be sure the tip of the needle is not in a vessel. The technic of administration is essentially the same as in subcutaneous injection. A 22-gauge needle about 2 inches long is used.

6. **Intraperitoneal Administration.**—This form is indicated in small children who have small veins, or those too old for sinus puncture, the fontanels having closed.

Method: Under sterile conditions a small slit is made in the skin of the abdomen a little below and to the left of the umbilicus; then a dull needle is introduced through this slit. Bladder should be empty to prevent puncture. Solutions of saline and dextrose up to 300 cc. may be introduced.

7. **Intramedullary Injections.**—Drugs administered by injection into bone marrow spaces by this route are absorbed rapidly, about as rapidly as by the intravenous route. It may be used for the infusion of liquids, and in infants for puncture of the femur or tibia. There is some danger of fat embolism and osteomyelitis.

8. **Subdural Injections.**—Subdural injections, also called subarachnoid or intrathecal injections, mean introduction of material into the cerebrospinal fluid. This method is used if the drug is to act directly on the spinal cord or on nerve roots as for spinal anesthesia. It is used also for colloidal drugs that do not penetrate the nervous tissues from the blood, e.g., arsphenaminized serum in cerebral syphilis.

a. *Lumbar Puncture.*—For this injection the patient should lie horizontally upon one side, the skin should be thoroughly cleansed with tincture of iodine and alcohol, and the needle pointing directly forward and slightly cephalad is introduced in the midline between the third and fourth lumbar vertebrae. The fourth lumbar vertebra may be distinguished by the fact that it is crossed by a line drawn between the two postiliac spines. A pressure greater than 200 mm. of water is to be regarded as abnormal. Estimate pressure only when patient is lying down; the pressure is higher when in an upright position. It is advisable to withdraw the spinal fluid slowly. For therapeutic purposes,

in the presence of increased spinal fluid pressure, not more than 20 cc. (in children 5 to 10 cc.) should be withdrawn, and the pressure should never be lower than 100 mm.

b. *Cistern Injection.*—This procedure requires no hospitalization, is easier for the physician, and has no undesirable effects. The patient sits with head flexed and supported on a pillow, then the needle is introduced just above the margin of the spinous process of the epistropheus (second cervical) through the ligamentum nuchae along the arch of the atlas to the foramen magnum and then through the dura into the cisterna cerebellomedullaris.

c. *Ventricle Injection.*—This procedure consists in trephining, under anesthesia, then the introduction of a cannula into the lateral ventricle.

9. **Inhalation Administration.**—This method is used for certain highly volatile drugs, e.g., ether, chloroform, and nitrous oxide. These are readily absorbed through the mucous membrane of the respiratory tract. The systemic action of these drugs is regulated by the concentration of the medication in the inspired air. The rich capillary area of the alveoli presents an excellent absorbing surface. Less volatile drugs are sometimes inhaled for their local action, e.g., medicated steam. Nonvolatile, finely divided substances may be absorbed from the respiratory tract sufficiently to develop a general action.

Inhalation has been used with some success for the administration of the sulfonamides and the antibiotics and for drugs used in the treatment of asthma.

Topical Administration

10. **Local Applications.**—Drugs may be applied directly to the skin or to mucous membranes. The vehicle and the method of application play an important part in the success of this type of medication.

Drugs may be administered to the skin, wounds, and mucous membranes in the form of ointments for prolonged action and protection; as plasters for prolonged action, protection, and mechanical support; in solutions for antiseptic purposes and moist dressings, and finally as dusting powders and poultices. Absorption from the skin is poor and uncertain. The lining of the sweat glands and the hair follicles offers the chief route of absorption for drugs in the normal skin.

a. *Inunction Administration.*—Inunction, or the introduction of a drug through the unbroken skin, in the past was frequently employed in the administration of mercury. Two other drugs, however, belladonna and codeine, may be profitably administered by this method. Mercury, administered by inunction, is often used in the treatment of syphilitic infants. Belladonna may be employed as a means of stopping lactation in a mother who is weaning her child.

b. *Intracutaneous Injections.*—These are injections made into the skin, and are used for making diagnostic skin tests, and also for local "infiltration anesthesia."

c. *Subnasal Injection.*—This means injection under the mucous membrane of the nasal septum. This gives rapid absorption (approaching the intravenous route).

d. *Application to Mucous Membranes.*—Aqueous solutions of drugs are generally used because oily liquids are rarely absorbed by mucous membranes. Warm isotonic solutions should be used and applied frequently.

e. *Nasal Medication.*—Gases, sprays, irrigations, and powders may be administered to the nasal mucosa. A warm fluid may be dropped in by means of a medicine dropper. Oils may be used for oil-soluble rem-

edies. The practice of administering oily nose drops has met with disfavor because of the possibility of producing a *lipoid pneumonia.*

Irrigation with large quantities of fluid is quite effective but care must be exercised to use fluid under low pressure, otherwise there is liability to infection by way of the eustachian tube. A mixture consisting of 25 per cent each of lanolin and petrolatum forms a useful base for nasal ointments.

Nasal medicaments, to be in line with present-day standards, should be isotonic, have a slightly acid reaction (pH 6.2), and be buffered to preserve the normal acid reaction of the nasal mucosa, to restore and preserve ciliary activity (Fabricant, 1942).

f. *Oral and Pharyngeal Administration.*—Troches, mouthwashes, gargles, irrigations, and local applications are the most common forms of medication used. *Troches* are slowly soluble medicated candies that have a soothing effect on the mouth and throat. *Mouthwashes* are usually sweetened solutions of alcohols, soaps or mild disinfectants, flavored with peppermint, cloves, etc., to make the taste more pleasant. They no doubt have little antiseptic value and are beneficial only as mechanical agents to remove foreign material. *Gargles* are usually astringents and are of value for adults if really brought in contact with the diseased tissue. *Irrigation* is especially valuable in treating children with scarlet fever. In this treatment a warm physiological saline solution is run back into the child's throat as it lies, face downward, on the nurse's lap. These irrigations are made between respirations.

g. *Urethral Administration.*—Lotions and suppositories are used in the urethral administration of drugs. Mild lotions may be used only on urethral mucosa. Small amounts may be administered to certain portions of the urethra, e.g., in chronic posterior urethritis. Large quantities may be used in urethral irrigations in late gonorrhea. Suppositories of medicated glycerogelatin, which melt soon after application, are often used in venereal prophylaxis.

h. *Vesical Medication.*—Irrigation of the bladder is used in chronic cystitis. As a rule a catheter is introduced, under sterile conditions, until urine escapes, then 100 to 200 cc. of fluid are injected into the bladder and left in for a few minutes.

i. *Vaginal Administration.*—Lotions, douches, and irrigations are commonly used in vaginal medication. The vaginal membrane is not easily irritated and will tolerate a fairly strong disinfectant, but since the vaginal mucosa readily absorbs drugs, care must be exercised in the choice of medication used.

In the healthy woman medication, such as douches, etc., is unnecessary, as the normal secretion and flora tend to promote cleanliness. A prolonged hot douche (105° to 115° F.), for 20 to 30 minutes, improves the circulation in the pelvic organs, hastens absorption of the exudate, and aids any inflammation of the parts.

Ulcers, erosions, and bleeding areas may be painted with 5 per cent silver nitrate.

j. *Conjunctival Administration.*—Only mild agents may be used in the conjunctival sac, but strong remedies are used locally. *Eye lotions,* such as 2 per cent boric acid, are used. Subacute or chronic conjunctivitis is often treated by using a 1:1,000 solution of zinc sulfate in 1 per cent sodium chloride.

Eyedrops commonly used are composed of 0.5 per cent atropine in an aqueous solution of 0.25 per cent salicylic acid. *Eyebaths* are carried out by using a 3 per cent boric acid solution and a suitably shaped eyecup. *Eye compresses* are indicated in the treatment of inflammatory processes of the eyelid, e.g., hordeolum. *Eye salves* or ointments are also

of value in the treatment of the eye. For example, petrolatum may be of value in preventing the eyelids from sticking together and yellow mercuric oxide ointment is valuable for preventing the recurrence of hordeolum.

ABSORPTION, DISTRIBUTION, FATE, AND EXCRETION OF DRUGS

ABSORPTION.—The time required for absorption of drugs into the body ranges from a few seconds, e.g., amyl nitrite, to several weeks, e.g., lead. The *rate of absorption* depends to a certain extent upon such factors as the solubility and diffusibility of the drug, and the health and permeability of the tissues through which the material passes. The site of administration and the efficiency of the circulation also influence the rate of absorption.

Drugs are most rapidly absorbed from serous surfaces such as those of the pleura and peritoneum. The subcutaneous tissues are next in efficiency, followed by the mucous membranes of the gastrointestinal tract.

When drugs are given by vein the factors concerned in absorption are eliminated and in most cases the action of the drug is immediate. Few drugs readily penetrate the skin. Certain fatty vehicles, however, greatly enhance cutaneous absorption. Drugs are rapidly absorbed when injected into muscular tissue.

A drug must be soluble before absorption takes place. Many drugs, which are apparently insoluble, are made more soluble after administration. For example, protamine zinc insulin, which is an insoluble suspension, gradually passes into solution in subcutaneous tissue, and absorption proceeds slowly over a long period of time.

Vascularity at the site of drug administration is an important factor influencing the rate of absorption. Inadequate circulation greatly retards absorption. Epinephrine, incorporated in injections, produces vasoconstriction and thus retards absorption. On the other hand, hyperemia aids absorption of drugs.

DISTRIBUTION.—After absorption in the blood stream the drug passes into the body fluids. Certain cells, according to their permeability and physical and chemical affinities, seem to attract drugs and will contain a higher concentration of that drug than do other tissues of the body. The digitalis glucosides are stored in much higher concentration in the cardiac muscle than elsewhere in the body. Lead is precipitated in bone, arsenic is stored in liver. Alcohol is fairly uniform in its distribution in body tissues. Sulfanilamide is an excellent example of a drug which is distributed throughout all the body fluids.

FATE OF DRUGS.—After absorption in the body drugs are more or less changed; some are rendered less harmful while others become more toxic. Some are rendered more effective therapeutically, e.g., sulfanilamide. The changes produced are effected by oxidation, reduction, decomposition, hydrolysis, cumulation, or by combination with other substances (synthesis).

The body employs various synthetic methods to detoxify drugs: (1) combination with glycocoll, e.g., benzoic acid; (2) combination with sulfates, e.g., phenol; (3) combination with glycuronic acid, e.g., sodium salicylate. The liver is the chief organ of defense against the absorption of toxic substances from the gut. It detoxifies many substances and fixes other substances which it cannot detoxify. The ability to fix toxic materials is one reason why large quantities of many poisons produce serious liver injury. The kidneys also store,

excrete, and even synthesize drugs. For example, in the kidneys benzoic acid and glycocoll form hippuric acid.

EXCRETION OF DRUGS.—The most common methods of removal of drugs are by excretion through the urine and feces, and with volatile drugs through the lungs. Excretion, like absorption, is usually more rapid with volatile and diffusible substances and with substances soluble in water. However, the specific chemical nature and affinity of the drug greatly influence rate of excretion. Drugs are excreted either unchanged or as simpler chemical compounds or in combination with some products of the organism. For example, ether is excreted by the lungs apparently unchanged. In the saliva are excreted small amounts of mercury, iodides, lead, potassium, menthol, morphine, quinine, etc. Morphine is excreted chiefly by the stomach and intestines; strychnine is excreted in the urine. Iodides, bromides, borates, phenol, salicylates, antipyrine, arsenic, mercury are some of the drugs excreted by sweat. The rapidity of excretion is proportional to the circulation and to the functional activity of the excretory organs, but may be modified by factors which affect these organs.

Many organic substances, such as alcohol, chloroform, and methenamine, pass to the *cerebrospinal fluid* and occur there in about the same concentration as found in serum. Inorganic substances are found in only minute quantities.

The following more important drugs have been demonstrated as passing to the fetus: chloroform, ether, carbon monoxide, atropine, morphine, scopolamine, chloral, quinine, benzoic acid, alcohol, nitrate, urea, arsenic, mercury, potassium iodide, and potassium bromide. Colloidal materials do not pass through the placenta into the fetal circulation.

MECHANISMS OF DRUG ACTION

No ready explanation is available to enlighten us on the manner in which many drugs exert their actions. Obviously, some drugs may exert their effects on a physical basis, e.g., the action of bismuth subcarbonate given in diarrhea coats the mucous membrane of the bowel and soothes and protects it. Drugs may act chemically, e.g., neutralization of gastric acidity by sodium carbonate. The efficacy of mercuric chloride as an antiseptic lies in the ability of the mercuric ion to precipitate the bacterial protein.

Many drugs are active by virtue of their ability to interfere with some metabolic process essential to the normal activity of the cell. It is now known that many chemicals, such as the sulfonamide drugs, act by interfering with useful metabolites, particularly vitamins, through competition involving similarity of chemical structure. Ephedrine inhibits the destruction of sympathin by combining with the enzyme amine oxidase.

Certain drugs exert their action by supplying an essential cell constituent, e.g., vitamins, hormones, minerals, and others. Of great significance is the fact that certain synthetic compounds can substitute for natural ones in the body, such as diethylstilbestrol, menadione and methacholine.

Many theories have been advanced to explain the mechanism of ether and other drugs on the central nervous system—none are satisfactory. We do not know how digitalis stimulates the fibers of the heart nor why pilocarpine has an affinity for secretory nerve endings.

Most of the current theories regarding the mechanism of drug action involve surface phenomena, including surface tension, polarity template effects, blocking effects, and competitive effect involving essential metabolites in complicated enzyme systems. Unfortunately space will

not permit an exhaustive review of these studies, and probably such information would be of little practical value to the average practitioner.

An important point for the physician to remember is that drugs produce their activity on the living organism by increasing or decreasing one or more functions. A drug tends to affect the extent of a cell's activity quantitatively but not qualitatively. Thus no drug can cause a salivary gland or a mammary gland to secrete gastric juice, the only effect being either to stimulate or to depress their normal activity. The degree to which drugs stimulate or depress can be controlled by dosage. The physician should always aim to secure from medication the degree of stimulation or depression that the circumstances warrant. No drug should be administered unless there exists a clearly defined physiological need for the specific action that that particular drug will produce.

Selective Action of Drugs.—The action of drugs is greater on some tissues than on others. Thus, some act on the heart only, others on the central nervous system, while others act on the terminations of motor nerves of muscles. This difference may be quantitative, but in some instances may be specific, e.g., a drug may have a powerful action on the brain but may have no effect on the heart. A drug may act entirely different on various structures. For example, atropine stimulates the brain but it depresses certain nerve endings; curare stimulates the spinal cord but paralyzes motor nerve endings.

Our present knowledge offers no explanation for the highly selective action which characterizes many of our important drugs. Because of this "selective action" it is often possible to treat one tissue without interfering with the function of others.

The complexity of the reactions taking place in cells is described in the following words by Sollmann:

"The living cell may be considered a very complex laboratory, where chemic decomposition and syntheses, reductions and oxidations, etc., are constantly going on. These chemic changes lead to transformations of energy which find expression in the phenomena of life. The vital manifestations of the cells are, therefore, inseparably connected with physicochemical transformations, which require for their occurrence the existence of certain chemic and physic conditions. The chemic essentials are: the presence of substances capable of liberating energy, and the conditions suitable for their reactions, such as a proper temperature, alkalinity, presence of ferments, etc. The physical conditions of life are: a viscid medium, containing colloid proteins, salts, fats, and water."

We must conclude that the activity of drugs depends on a large variety of factors, and that pharmacological action cannot be completely explained by any one physical or chemical process.

CONDITIONS MODIFYING DRUG ACTION

The conditions that modify the effects of drugs on the living organism should be recognized by the physician and the dosage adjusted accordingly. The following are some of the important conditions which modify drug action:

1. **Dose.**—The pharmacologic response obviously tends to increase with the concentration of the drug, but not generally in simple proportion. The *minimal therapeutic dose* is the smallest amount which will produce a therapeutic effect. The *maximal therapeutic dose* is the largest amount that can be tolerated without toxic effects. The *therapeutic dose* lies somewhere between the maximal and minimal doses.

2. **Solubility of Drug.**—Only soluble drugs can be absorbed and cause general action; local action of drugs may occur without absorption.

3. **Size and Weight.**—A very large individual requires a larger dose than persons of average weight, while smaller individuals require smaller doses than a person of normal weight. The proportions of fat and muscle should be taken into consideration. Very obese persons, though heavy, react usually like those of lesser weight, but more muscular. Fat persons may require a greater amount of lipoid soluble drugs than their weight would indicate. Pathological growths or collections of fluids do not indicate a change in dosage but a person so afflicted should receive an amount based on his natural weight.

4. **Age.**—Children and the aged should receive smaller doses than young adults, as they are usually more susceptible to the action of drugs. There are, however, exceptions to this rule; for example, children usually require more digitalis than the dosage rules indicate, while older persons often react to atropine, developing a type of atropine psychosis.

5. **Sex.**—Women generally require smaller doses than men, due chiefly to their smaller weight, and in part due to their different physical and mental make-up. Certain drugs may have a direct or indirect influence upon the menstrual function of the female. Pregnancy may necessitate a change in the dose of a drug and also alter the response of the female to the drug. During pregnancy and lactation great care should be exercised in the administration of purgatives, diuretics, and very active drugs. Women may respond to opium and its derivatives with excitement instead of depression.

6. **Idiosyncrasy to Drugs.**—Idiosyncrasy means any marked individual difference in reaction to drugs. A. F. Coca states that there is practically no basic difference between drug allergy and other forms of idiosyncrasy. The basic processes are probably similar or identical.

More recently, evidence has been brought forward to indicate that drug idiosyncrasy may be of an allergic, or, in some instances, that of a nonallergic, nature. The untoward reactions of acetylsalicylic acid appear to be allergic in all instances, and a large number of the sulfonamide and penicillin reactions appear to be on an allergic basis. There is reason to believe that a variety of drug idiosyncrasies may depend on nonallergic factors, and in many cases some drugs may produce both allergic and nonallergic types of toxic reactions.

The following provisional criteria has been suggested by C. A. Dragstedt (1947).

1. "An allergic basis seems to be indicated when the pattern of the toxic reaction is consistent with that of the allergic disorders produced by antigenic agents. This means that reactions characterized by urticaria, dermatitis, angioneurotic edema and asthma are probably allergic in character; that reactions characterized by jaundice, acute yellow atrophy of the liver and optic atrophy are probably not allergic, while granulocytopenia, anemia, thrombocytopenia and polyneuritis may well be one or the other.

2. "An allergic basis seems to be indicated when a priming or sensitizing administration of the drug appears to be a factor in the history, while a nonallergic basis seems to be indicated when either long-continued administration or the use of substantial doses appear of major importance.

3. "An allergic basis seems to be indicated when the untoward reactions are alleviated by epinephrine, diphenhydramine hydrochloride ("benadryl hydrochloride" N.N.R.) and similar agents, whose ameliorating effects are most reasonably interpreted on the basis of an antiallergic effect. A nonallergic basis seems to be indicated for those reactions which are alleviated by ascorbic acid, folic acid, thiamine and other agents whose ameliorating effect is not reasonably credited to an antiallergic effect."

A person who is sensitive to various drugs may react to entirely different drugs pharmacologically with the same symptoms. A person allergic to one drug is likely to be sensitive to many drugs. This type of person is usually made worse by all forms of medication.

Drugs may cause reactions following absorption through direct contact with the skin, but most drugs exert their action after penetration of the tissues. The symptoms may be similar to those found in the common allergies, including fever, edema, skin eruptions, urticaria, asthma, coryza, migraine, gastrointestinal upset, and occasionally shock. Some drugs produce characteristic symptoms of their own which aid in diagnosis. The patient's individual make-up and the route of administration influence the nature of the symptoms.

The drugs which are most liable to produce untoward reactions include aspirin, quinine, the arsphenamines, aminopyrine, sulfa drugs, cinchophen, sulfur, barbiturates, sulfocyanates, iodine, and many more.

There is no reliable diagnostic test for drug allergy. *Skin tests* are unreliable, with the possible exception of plant drugs, aspirin and quinine. The *ophthalmic test,* made by instilling one or two drops of a solution of the drug to be tested in the conjunctiva, is more reliable. The simplest *treatment* is to avoid the offending drug. A substitute may be employed, but sensitization to the substitute may occur. Desensitization may be successful. Acute symptoms may be temporarily relieved by epinephrine and its related compounds.

7. **Tolerance.**—Tolerance is the acquisition of a relative insusceptibility to the action of a drug. This ability to endure the continued or increasing use of a drug may be due to nonabsorption, to destruction of the drug, to increased elimination, or it may be due to production of antibodies. Tolerance is, with some individuals, readily established for such drugs as opium, cocaine, coal tar derivatives, alcohol, and tobacco.

a. *Congenital tolerance* is the failure of the individual to react to the normal dose of a drug. An example is the tolerance shown by rabbits for large quantities of atropine.

b. *Acquired tolerance* is a form of tolerance induced by prolonged use of a drug. The most familiar example of this form of tolerance is that acquired for tobacco (nicotine). The prolonged use of opium develops a tolerance for the drug. This tolerance usually is lost if the drug is discontinued for some time, then upon continuing the use of the drug a smaller amount is sufficient to produce the same degree of action as was produced when use of it was stopped. Prolonged use of one drug may establish tolerance for others of the same class. Chronic alcoholics are little affected by average doses of alcohol, and they are more resistant to ether than are ordinary persons. This action is explained as being due to the similarity of action of alcohol and ether on nerve cells.

8. **Synergistic Action.**—Certain drugs having the same therapeutic action, when given together, produce a combined effect greater than the summation of their individual actions. This greater combined

action is called *synergistic action,* and the drugs which act in this manner are called *synergists.* Purgatives, anesthetics, and narcotics frequently evidence synergistic effects. Several purgatives given together may act more effectively than any one given in quantity equal to all of them. This may be partially explained on the basis that there is some difference in the type of reaction produced, thus making the mixture more efficient than any one of its components.

9. **Antagonistic Action.**—Some drugs when used together seem to have their effects partially or wholly neutralized. The drugs which produce this action are called *antagonists* and should not be prescribed together. Opium preparations and vegetable cathartics exert antagonistic effects on the intestines, atropine neutralizes the effect of pilocarpine on sweat glands, and caffeine neutralizes the depressive effects of morphine. In poisoning, the antagonistic action of drugs is made use of to prevent or neutralize toxic action. In poisoning from a depressant a stimulant should be administered.

10. **Cumulative Effect.**—This is a condition characterized by sudden pronounced manifestations of drug action following the administration of a number of doses of drugs over a period of time. It may be due to accumulation, to irregular absorption, summation of effects from repeated doses, or be due to a general decrease in resistance or ability of the body to handle the drug. Some of the drugs which produce temporary cumulative action include digitalis, atropine, strychnine, arsenic, and iodides.

11. **Habituation.**—Habituation usually lessens the pharmacologic effect of drugs; however, in a few cases, e.g., cascara, the action increases with use. In some cases the tissues become adapted to the presence of certain drugs and are unable to function properly without them. This condition is well illustrated in cases of opium, heroin, and cocaine addiction. Habituation may be functional, as suggested for marihuana; or it may be due to diminished absorption, as shown by arsenic; or the condition may be due to increased elimination, as with atropine; or due to increased destruction to the poison, as with morphine; or finally, habituation may be due to the production of antibodies. Habituation may be largely psychic in habit-forming drugs; here the nerve centers are adjusted to the action of a drug and when this drug is withdrawn there follow symptoms of extreme discomfort.

12. **Speed of Administration.**—The speed or rapidity of administering drugs may spell the difference between life and death. Any drug administered by vein should be properly diluted, and given very slowly. Quinine solutions, when indicated in malaria, should be administered very slowly and in dilute form when administered intravenously; otherwise they may produce a stoppage of the heart. Many ill effects of salvarsan, following intravenous injection, are due to rapid injection.

13. **Time Element in Drug Action.**—The time element plays an important role in pharmacological action. Taking into consideration the effect of both time and concentration on drug action Hubner made the following generalizations. He divided drugs into three groups.

GROUP I. In this group pharmacological reactions may be expressed by the equation:

$$W = C$$

W Action of drug
C Concentration (dosage)
T Time element

The drugs of this group exert their action without special reference to time (T). *Example.*—Ether: In order to induce general anesthesia ether must be inhaled in a concentration which induces a definite tension of the gas in the blood, sufficient for anesthesia of the brain. For light anesthesia the concentration of ether in the respired air must be 6 per cent by volume, for deep anesthesia 10.5 per cent. The action of ether is directly proportional to the concentration in the blood or to the tension of the ether vapor in the blood.

GROUP II. In this group of drugs the action may be expressed by the following formula:

$$W = C \times T$$

The toxicity of these drugs is increased in proportion to length of time administered.

Example 1. Chloroform anesthesia requires a given concentration of gas in the respired air; general anesthesia cannot be safely maintained more than one hour. The action of the drug (W) is proportional to its concentration (C) in the blood and also is increased with the time (T) over which it is administered.

Example 2. Digitalis cannot be administered indefinitely. Active principles of digitalis form chemical combinations with the cardiac muscle. These combinations are slowly destroyed; after saturation of the muscle additional doses produce toxic rather than therapeutic results.

Example 3. Mercurochrome's antiseptic action is exerted over a long period of time because of the presence of the free drug in the deep stain. There is no chemical action between tissues and the drug.

GROUP III. In the third group of drugs the action may be expressed as follows:

$$W = \frac{C}{T}$$

Here the time element is involved. Instead of time increasing the potency of the drug, it decreases it inversely to the length of time over which it is administered.

Example 1. Arsenic may be taken in small doses producing habituation, but large doses are required to produce a pharmacological effect.

Example 2. Iodine, as an antiseptic, is powerful at first, but its bactericidal effects rapidly diminish. The decreased action is inversely proportional to the time elapsing after it is administered.

14. **Route of Administration.**—The glucoside amygdalin, given by injection, produces no harmful effects; when it is administered orally (in the rabbit), the glucoside is hydrolyzed, setting free hydrocyanic acid which usually causes death.

Magnesium sulfate, administered orally, is a useful saline cathartic; given by vein, or even subcutaneously, there is produced a powerful depression of the central nervous system.

It is important to remember that the route of administration profoundly modifies the dose effect. Absorption is slow through the skin and most rapid when the drug is given by vein.

15. **The Subject to Which a Drug Is Administered.**—The student of pharmacology must learn that data obtained from animals cannot be applied, without reservation, to man. For example, a rat and mouse react differently to morphine; a toad is more resistant to digitalis than a frog. Organs may vary in their response to drugs; epinephrine produces contraction of most blood vessels but dilates the coronary vessels.

Racial differences influence drug action, e.g., castor oil is used as a food in China; ephedrine dilates the pupil of the yellow race but the mydriasis produced is slight in the white race. Animals react differently to drugs; e.g., a rabbit requires 50 times as much morphine to produce poisoning as is required for a man; a goat is resistant to nicotine; a hedgehog is resistant to snake venom and even hydrocyanic acid. These drugs are lethal for most warm-blooded animals.

16. **Temperature.**—Temperature influences drug action, the effect of most drugs being more intense at higher temperatures. Kassa found that he could inject cyanides into a rabbit's ear with no ill effects at low temperatures, but poisoning resulted at warm temperatures. Pigeons, when cold, are little affected by morphine and apomorphine, but vomit when brought to a warmer temperature. Colchicine is not poisonous to a frog kept on ice, but poisons the frog when the animal is brought to a warm, dark room. This is due to the formation of oxydicolchicine. Purgatives act more effectively in hot weather. Antipyretics tend to reduce the temperature of the body in fevers, while under normal conditions they are usually ineffective.

17. **Bacteria and Enzymes.**—An important role may be played by bacteria and enzymes. Bismuth poisoning may result from bacteria or enzymes acting on the insoluble salts, forming toxic soluble bismuth compounds.

18. **Disease and Pathological Conditions.**—Disease and its associated symptoms are often important factors in determining the dose of a medicine, and the frequency of its administration. For example, if the routes of excretion are altered by disease the repetition of the dose need only be at comparatively long intervals. Response to drug action in the diseased state is variable. Bromides lessen nervous irritability in epilepsy to a greater extent than they do in the normal state. Quinine is tolerated in much greater doses in the presence of malaria than in the absence of this disease. Morphine is tolerated well in conditions of extreme pain. Digitalis will exhibit beneficial properties for the myocardial muscle only when the heart muscle is abnormal, e.g., in the weakened heart, arrhythmia, etc.

In Conclusion: Probably of the above conditions the *most important factors modifying drug action* are dosage, ratio of drug absorption to rate of excretion (or destruction), the physical-chemical properties of drugs, and the individual response to the drug administered. Leake (1948) has suggested the following formula to show the relationship of these factors to the intensity of drug action.

$$I = (f)\, D \frac{rA}{rE}, P.S.$$

I = intensity of drug action
D = dosage (mg. drug per Kg. body weight)
rA = rate of absorption
rE = rate of excretion
P = physical-chemical properties of drug
S = individual response (or idiosyncrasies) to drug by patient

What You Should Know About Drugs

In the treatment of disease the diagnosis comes first, then the decision by the physician regarding what drug should be administered to bring about the desired results in the patient. Drugs are the most useful and effective therapeutic measures at the physician's command.

The physician must remember, however, that in order to secure success with a drug—the remedy must be *properly indicated,* the preparation selected must be *active,* and an *effective therapeutic dose* must be administered.

A matter of prime importance in the use of drugs in medicine is to weigh the hazards of the drug against the hazards of the disease. The physician should, of course, know in advance what symptoms my appear in case of toxic action and be prepared to treat them promptly.

In order to select and administer a drug wisely the physician should know the following:

The names of drugs and their preparations.
The active constituents.
Solubilities and incompatibilities.
Dosage.
The Pharmacological Action:
    How the drugs act.
Toxicology:
    Symptoms of poisoning.
    Treatment of poisoning.
Practical Application (Therapeutics):
    Indications for use.
    What drug to use.
        How much and how to administer the drug.
        When to stop the drug.
    Contraindications.
        When not to use the drug.
    How to write prescriptions.

References

Bernheim, F.: The Interaction of Drugs and Cell Catalysts, Minneapolis, 1946, Burgess Publishing Co.

Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 3, Baltimore, 1943, Williams & Wilkins Co.

Bodansky, Myer, and Bodansky, Oscar: Biochemistry of Disease, New York, 1941, The Macmillan Co.

Calvery, H. O., Draise, J. H., and Lang, E. P.: The Metabolism and Permeability of Normal Skin, Physiol. Rev. 26: 495, 1946.

Chemistry and Medicine, Papers Presented at the Fiftieth Anniversary of the Founding of the Medical School at the University of Minnesota. M. B. Visscher, Editor; Minneapolis, 1940, University of Minnesota Press.

Clark, A. J.: Mode of Action of Drugs on Cells, Baltimore, 1935, Williams & Wilkins Co.

Clark, A. J.: General Pharmacology—Supplement IV to Heffter's Handbuch der experimentellen Pharmakologie, Berlin, 1937, Springer.

Dragstedt, C. A.: Idiosyncrasy to Drugs, J. A. M. A. 135: 133, 1947.

Fabricant, N. D.: Nasal Medication, Baltimore, 1942, Williams & Wilkins Co.

Fantus, B.: The Technic of Medication, Chicago, 1926, American Medical Association. (Dr. Austin Smith, Secretary of the Council on Pharmacy and Chemistry, has prepared a new edition of this useful practical guide.) General Technic of Medication, Chicago, 1948, American Medical Association.

Findlay, A.: Physical Chemistry for Students of Medicine, London, 1927, Longmans, Green & Co.

Findlay, G. M.: Recent Advances in Chemotherapy, ed. 2, Philadelphia, 1939, P. Blakiston's Son & Co.

Gaddum, J. H.: Principles of Administration in Chemotherapy, Brit. M. Bull. **4**: 280, 1946.

Gruber, C. M.: Handbook of Treatment and Medical Formulary, Philadelphia, 1949, F. A. Davis Co.

Hopkins, J. G.: Some Newer Bases for Use in Cutaneous Therapy, J. Invest. Dermat. **7**: 171, 1946.

Hurst, H.: Biophysical Factors in Drug Action, Brit. M. Bull. **3**: 132, 1945.

Lane, C. H., and Blank, I. H.: Vehicles in Topical Dermatologic Therapy; Their Functions and Physicochemical Characteristics, Arch. Dermat. & Syph. **54**: 650, 1946.

Leake, C. D.: Current Pharmacology—General Principles in Practical Clinical Application, J. A. M. A. **138**: 730, 1948.

MacKee, G. M., Sulzberger, M. B., Herrmann, F., and Baer, R. L.: Histologic Studies of Percutaneous Penetration With Special Reference to the Effect of Vehicles, J. Invest. Dermat. **6**: 43, 1945.

Prigal, S. J.: The Production of Aerosols From Medicated Solutions, J. A. M. A. **131**: 398, 1946.

Quilligan, J. J., Jr., and Turkel, H.: Bone Marrow Infusion and Its Complications, Am. J. Dis. Child. **71**: 457, 1946.

Steel, M.: Physical Chemistry and Biophysics for Students of Biology and Medicine, New York, 1928, John Wiley and Sons, Inc.

Tr. Faraday Society: Modes of Drug Action **39**: 319-444, 1943.

Woolley, D. W.: Recent Advances in the Study of Biological Competition Between Structurally Related Compounds, Physiol. Rev. **27**: 308, 1947.

CHAPTER II

MATERIA MEDICA

Materia Medica.—Drug remedies are known collectively as the "materia medica" or medical materials. Materia medica is a science which deals with the study of sources, constituents, physical and chemical characteristics, preparations, and dosage of medical materials. This subject is studied in more detail in courses in pharmacy but a knowledge of the essential features is of importance to students of medicine.

Galenical Preparations. These are medicines prepared according to the formulas of Galen. The term is now used to denote standard preparations containing one or several organic ingredients made by physical, as distinguished from chemical, means, such as tinctures, infusions, etc.

Proprietary Drugs. "Any chemical, drug, or similar preparation used in the treatment of disease, if such article is protected against free competition as to name, product, composition, or process of manufacture by secrecy, patent, or copyright, or by any other means." (A.M.A.)

Patent Medicines. These are proprietary drugs that are advertised to the laity.

Official Drugs. Drugs and preparations which are found in the current U.S.P. or the N.F. are spoken of as "official."

The student of medicine should become familiar with and consult regularly the following publications:

The United States Pharmacopoeia, U.S.P. This publication is controlled by the United States Pharmacopoeial Convention, which is incorporated under the laws of the District of Columbia for the purpose of issuing the Pharmacopoeia. The U.S.P. Convention consists of delegated members from colleges of medicine and pharmacy and incorporated medical, dental, and pharmaceutical organizations.

The object and scope of the Pharmacopoeia is set forth in the following quotation from the U.S.P.:

"The object of the Pharmacopoeia is to provide standards for drugs and medicines of therapeutic usefulness or pharmaceutical necessity, sufficiently used in medical practice within the United States or its possessions; to lay down tests for the identity, quality, and purity of these; to insure, so far as practicable, uniformity in physical properties and active constituents."

The first U.S.P. was published in 1820. The thirteenth edition became official on April 1, 1947. The Pharmacopoeia is recognized in courts of law as being the ultimate standard reference for those drugs that are listed in it. The thirteenth edition lists English names for drugs and the metric system for dosages giving preference over Latin names and the apothecaries' system. This book has been revised and issued every ten years under the supervision of a national committee. Under the present policy revision will take place at five-year intervals. Supplements will be published from time to time to include new preparations.

The British Pharmacopoeia, B.P. was first published in London in 1864. It is now in the sixth edition (1932) with seven supplements

covering recent changes. This pharmacopoeia is published by the General Medical Council and resembles the U.S.P.

The *United States Dispensatory* (U.S.D.) was first published in 1833. It is a nonofficial compilation and includes all items in the U.S.P., N.F., and B.P., as well as many nonofficial drugs. The U.S.D. is now in its twenty-fourth edition.

The National Formulary N.F., eighth edition. Prepared by the Committee on National Formulary. Authority of the American Pharmaceutical Association. Official April 1, 1947. Published by the American Pharmaceutical Association, Washington, D. C.

The book gives complete information on many drugs, chemicals, and preparations used in the practice of medicine. The exact composition, method of preparation, description, and average dosage for each preparation are given.

The second part of the book contains much valuable information concerning reagents and preparations used in clinical laboratories. Staining solutions, test solutions, and special techniques will also be found.

The National Formulary, in addition to being indispensable to the pharmacist, will be of much value to many physicians and should find a place in the modern medical library. Originally, the N.F. had no legal standing, but the Food and Drug Act of 1906 and the Food, Drug and Cosmetic Act of 1938 gave the N.F. the same official standing as the U.S.P.

New and Nonofficial Remedies, N.N.R. This is a book containing a description (action, uses, standards) of proprietary articles which have been found acceptable by the Council on Pharmacy and Chemistry of the American Medical Association. This book is an excellent guide to new therapeutic discoveries. If after a few years the value of the remedy is proved, it may be included in the Pharmacopoeia; if, on the other hand, such value is not shown, the remedy may be dropped from the book (N.N.R.). It is issued annually.

Accepted Dental Remedies, A.D.R., is a book similar to N.N.R., compiled by the Council on Dental Therapeutics of the American Dental Association. It contains items properly manufactured and truthfully advertised.

Useful Drugs. This is a small book issued by the American Medical Association which contains only the most useful drugs with information of special interest to physicians. It contains a select number of preparations from the U.S.P., N.F., and N.N.R. It may be of interest to know that no advertising in any of the American Medical Association's journals is permitted for nonaccepted products.

Epitome of the U.S.P. and N.F. This small book is also prepared by the American Medical Association. It gives a brief abstract of all U.S.P. and N.F. preparations.

Source of Drugs

Drugs are derived from the *mineral, vegetable,* and *animal* kingdoms. Recently many drugs have been synthesized. The ones derived from the mineral kingdom are known as inorganic drugs; those derived from vegetable and animal sources are organic drugs. There are more than 3,500 known inorganic drugs and more than 350,000 known organic preparations. It requires a very fine sense of discrimination on the part of the teacher to select the best therapeutic agents from this superabundance of drugs to present to his students.

A. Vegetable.—The active principles of plants form a large portion of our drugs. The following are the most important plant parts used for the manufacture of drugs:

1. ROOT *(Radix)*.—The underground achlorophyllous part, devoid of leaves (rhubarb, belladonna). Some roots are tuberous, being swollen with reserve material (aconite, glycyrrhiza, jalap).

2. BULB.—A modified stem with many thick and crowded overlapping leaves (onion, squill).

3. CORM.—A thickened fleshy underground stem (colchicum).

4. WOOD *(Lignum)*.—The wood of trees (quassia, sandalwood, hematoxylon).

5. RHIZOME.—An underground stem which bears leaves, buds, and roots (podophyllum, ginger, hydrastis, aspidium).

6. BARK *(Cortex)*.—The outer protective layer of the stem (cinchona, cascara, wild cherry). The outer layer of the root (sassafras, cotton-root); the inner bark (Ceylon cinnamon, elm).

7. LEAVES *(Folia)*.—Digitalis, belladonna, senna, hamamelis.

8. FLOWERS *(Flores)*.—Chamomile, arnica. Unexpanded flowers are cloves, santonica.

9. FRUIT *(Fructus)*.—Produced by the fertilized and ripened ovary (pepper, colocynth, anise).

10. SEED *(Semen)*.—The essential part of the fruit (nux vomica, strophanthin, physostigmine, linseed, theobromine).

B. Animal.—Drugs from animal sources are rapidly becoming of great importance in therapeutics. The endocrine glands are utilized for the preparation of insulin, pituitrin, adrenalin, pitocin, pitressin, theelin, and many more drugs of practical value to the medical profession.

Vaccines, sera, and vitamins are obtained from animal sources. Plants are considered the origin of most vitamins. Penicillin and other microbiotic agents are produced by bacteria and fungi.

C. Inorganic.—This group includes the metals, the metalloids, and nonmetals, together with many of their compounds.

D. Synthetic.—This group is large and contains an ever-increasing number of products of both an organic and an inorganic nature. New and Nonofficial Remedies contains a discussion of a great number of new synthetic compounds, including such compounds as thyroxin, diodrast, ipral, butesin, metycaine, vitamins, antithyroid drugs, and the sulfa drugs.

Composition of Drugs

Plants contain a great variety of substances of complex and often unknown composition. The important constituents may be classified as follows:

Alkaloids.—Among the most important of organic compounds employed in medicine are the alkaloids. They are found in almost all parts of plants, but in greatest abundance in the seeds and roots. These compounds are complex, basic nitrogenous organic compounds. Most of them are derived from plants but a few are animal products. They are relatively insoluble in water but soluble in ether, chloroform and similar organic solvents. Alkaloids are characterized by a bitter taste, optical activity, and marked physiological or toxic properties. They are precipitated by alkaloidal reagents; the more common of these agents are tannic acid, picric acid, phosphotungstic acid, and mercuric chloride in potassium iodide (Mayer's reagent).

It must be remembered that many of the alkaloidal compounds are deadly poisons. In prescribing alkaloids, it is well to remember that the free alkaloids are relatively insoluble in water, while, in contrast, the salts are soluble in water.

The chemical constitution of alkaloids varies greatly. The greater number of alkaloids are fairly complex derivatives of pyridine (coniine, nicotine); pyrrolidin (cocaine, atropine); quinoline (quinine, cinchonine); isoquinoline (hydrastine, narcotine, cotarnine, berberine); phenanthrene (morphine, codeine, thebaine).

Glycosides.—Next in importance to the alkaloids, among the vegetable drugs, rank the glycosides. These are combinations of sugars (usually glucose) with other substances, frequently phenols. They may be hydrolyzed by acids or certain enzymes into sugar and other substances. The two glycosides, amygdalin and sinigrin, which are almost inert pharmacologically, are of importance because of their products of decomposition.

Amygdalin, with its enzyme emulsin, occurs in bitter almonds, peach pits, and wild-cherry bark. In the presence of water the enzyme splits amygdalin into glucose, hydrocyanic acid, and benzaldehyde. A mixture of hydrocyanic acid and benzaldehyde constitutes the volatile "oil of bitter almond."

Sinigrin, with its enzyme myrosin, occurs in black mustard seed. In the presence of moisture the enzyme hydrolyzes sinigrin, yielding glucose, potassium bisulfate and allyl-isothiocyanate (volatile oil of mustard).

Starch.—This carbohydrate is an isomer of cellulose and possesses the empirical formula $(C_6H_{10}O_5)_n$. It occurs in the form of small characteristic granules within the chloroplasts of plant cells. Corn-starch (amylum) is commonly used in medicine.

Sugars.—Sugars are found widespread in the plant kingdom. They are soluble in water and alcohol, are optically active, and some have the power of reducing Fehling's solution. The most important are: glucose (dextrose) and levulose (fructose), $C_6H_{12}O_6$; maltose and saccharose, $C_{12}H_{22}O_{11}$.

Gums.—These are amorphous, colloidal, complex carbohydrates of the formula $(C_6H_{10}O_5)_n$. Some are soluble in water, while others swell to a jelly in it; they are insoluble in alcohol. They are formed in the plant by transformation of cellulose and cell contents, especially after pathological changes. They generally occur naturally in combination with calcium, magnesium, or potassium; they have no poisonous action but form a protective covering for irritated plant surfaces.

Cellulose.—This carbohydrate is found in the cell walls. It is insoluble in the ordinary solvents. The chemical formula is $(C_6H_{10}O_5)_n$. It may be modified to form cork and wood or hydrolyzed and modified to form gum or pectin. Pectin is a therapeutic agent of importance.

Tannins.—Some tannins are glycosides which on hydrolysis yield glucose and tannic acid. These are a class of phenol derivatives characterized by a bluish or greenish color which they give to ferric salts, and by their bitter taste. They precipitate alkaloids, mercuric chloride, proteins, and gelatin. They occur chiefly in the barks of trees, and in plant-galls which result from the punctures of insects. The various tannins are named according to their source, e.g., cinchotannic acid, kinotannic acid, etc. The U.S.P. tannic acid is derived from oak-galls.

Saponins.—These are neutral, nonnitrogenous substances characterized by foaming with water, emulsifying oils, and the laking of red

blood cells. They are of wide occurrence. Some are very toxic and are called sapotoxins.

Resins.—These constitute a heterogeneous group characterized by their insolubility in water, solubility in alcohol and most fat solvents, and solubility in alkalies. Common rosin, and the resins of guaiac, jalap, podophyllum and ipomoea are well-known resins.

Oleoresins.—These are neutral plant exudates which contain both oil and resin. Balsam of copaiba, Canada balsam, and crude turpentine are examples.

Gum-Resins.—These compounds are generally oleoresins in natural admixture with gum. Asafetida and gamboge are examples.

Balsams.—These compounds are resinous or oleoresinous exudates which contain benzoic or cinnamic acid or both. Benzoin, storax, balsam of Tolu, and balsam of Peru are examples.

Volatile Oils (Essential Oils).—These are volatile, alcohol-soluble, odorous principles found in plants. Chemically they are mixtures of esters, aldehydes, alcohols, ketones, and terpenes.

Fats and Fixed Oils.—Fats (esters of fatty acids and glycerin) are found abundantly in seeds. They are insoluble in water, sparingly soluble in alcohol, and freely soluble in fat solvents.

Waxes.—These compounds are esters of fatty acids with alcohols other than glycerin. They are solid substances with solubility characteristics of fats.

Proteins.—These compounds are found in all the plant cells. The proteins found in crude drugs are chiefly albuminous in nature. A few of the plant proteins, such as ricin from castor-oil seeds, and crotin from croton oil, are toxic.

Chlorophyll.—This is the green pigment of leaves; it is insoluble in water, but soluble in alcohol and in fat solvents. It is allied to hemoglobin but contains no iron. Chlorophyll is claimed to have certain local healing properties.

Enzymes.—A few enzymes obtained from plants are used in medicine. Papain is a digestive ferment obtained from the juice of the fruit of the papaw, *Carica papaya.*

Organic Acids.—The common organic acids include citric acid derived from citrus fruits, tartaric acid from grapes, and salicylic acid from willow bark.

Pharmaceutical Processes

Different methods are employed in preparing pharmaceutical products, depending on the character of the crude drug and upon the type of preparation desired. The following processes are commonly employed:

A. Preliminary Treatment.—It is usually necessary to dry the crude drug after collection. The material may be cut into smaller pieces and dried at about 35° to 40° C. A higher temperature may be injurious to some of the ingredients. After drying, the plant is ground to a powder. Powders are classified as to fineness by sifting through sieves of different sizes and meshes, thus:

No. 80 mesh: very fine—80 meshes to the linear inch;
No. 60 mesh: fine—60 meshes to the linear inch;
No. 40 mesh: moderately coarse—40 meshes to the linear inch;
No. 20 mesh: coarse—20 meshes to the linear inch.

For example, digitalis leaves are usually ground and sifted through a No. 60 sieve preparatory to percolating; however, for manufacturing digitalis tablets the powder should be fine enough to pass through a No. 80 or No. 100 mesh sieve.

B. Separation Processes.—The desired ingredients are separated from the inert material by three common processes:

1. HEAT.—If the constituents are volatile they may be separated by distillation. *Distillation* may be used to separate a volatile from a less volatile constituent. *Fractional distillation* may be used to separate mixtures of liquids of different boiling points. *Evaporation* may be used to remove the solvent from a solution, thus leaving a concentrated product. *Sublimation* may be used to separate a volatile from a non-volatile solid.

2. ACTION OF SOLVENT.—

Solution.—Various solvents may be employed to remove the desired active ingredients from the insoluble inert material. The object is to dissolve the greatest possible amount of active ingredients with the least possible menstruum. The most important *pharmaceutical solvents* are:

Alcohol: Alkaloids (salts), resins, volatile oils, glucosides, and neutral principles.

Water or Glycerin: Acids, alkalies, salts, sugars, gums, glucosides, and tannins.

Ether, Chloroform, or Acetone: Free alkaloids, neutral principles, resins, fats, volatile and fixed oils.

Dilute Acetic Acid: Alkaloids.

Petroleum Benzine: Free alkaloids, fats, volatile and fixed oils, and neutral principles.

Maceration consists in leaving the solvent in contact with the drug for a sufficient length of time to extract the desired substances.

Percolation consists in passing a solvent through a thick layer of powder in order to remove the soluble constituents. This is carried out by packing a tall vessel (percolator) with a hole in the bottom with the powder to be extracted, and then allowing the solvent to pass slowly through it.

Precipitation consists in the deposition of solids from their solvents by either physical or chemical means.

3. MECHANICAL MEANS.—*Expression* is the process of separating a liquid from a solid by pressure. Coarse solid particles may be separated from a liquid by *straining*. The process of *filtration* may be employed to separate insoluble particles from a liquid by pouring it through a finely porous material such as filter paper. Colloidal substances may be purified by *dialysis*.

Standardization of Drugs

After the active constituents have been removed from the crude drugs they must be standardized in order to be certain of uniformity of clinical response to the same dose of a drug.

When the active principles of crude drugs were isolated in chemically pure form, a great advance was possible in standardization, since now the crystalline substance could be made to conform to specific chemical standards. A more exact relationship between dosage and effect thus became possible.

In most cases the strength of a preparation may be determined by chemical methods, but in some cases biological means must be em-

ployed. The strength of unknown drugs or drug extracts is determined by pharmaceutical (chemical) or pharmacological (biological) assaying.

Pharmaceutical or Chemical Assays.—The chemical assay consists of the assaying of inorganic drugs, oils, alkaloids, organic drugs, etc. The assay of inorganic drugs involves the standard quantitative methods of analysis. The Pharmacopoeia furnishes methods for quantitative analysis, special tests to determine harmful substances, and methods for determining the possible limits of impurities. For example, thyroid should contain not less than 0.17 per cent and not more than 0.23 per cent of iodine in thyroid combination, and must be free from iodine other than that peculiar to the thyroid gland; nux vomica not less than 1.15 per cent of strychnine, to conform with the United States Pharmacopoeia for an "official drug." Fatty substances are analyzed chiefly for iodine number, saponification number, etc., in order to identify and to test for adulteration.

With some of the more complex synthetic drugs such as the arsphenamines and arsenoxides, only government licensees may manufacture the drugs. After manufacture, sample lots are tested for toxicity by the National Institute of Health.

Pharmacological or Biological Assays (Bio-assays).—Biological assaying, or determining the strength of a preparation by its effect on living animals or tissues, is resorted to for certain drugs whose constituents are insufficiently known, cannot be isolated quantitatively, and cannot be estimated by chemical means.

Biological assay was first introduced to measure the activity of drugs, such as digitalis, whose active principles could not be measured by chemical means. It involves difficult technic and is expensive, therefore it is employed only when absolutely necessary. The strength of the crude drug which is bio-assayed is usually expressed in *units*. Most official drugs have legally required methods of assay, and units which are universally recognized. Unfortunately, some of the newer preparations, notably certain endocrines, have no specified methods of assay or universally accepted units.

For biological assay, animals (frogs, cats, dogs, rodents, etc.) of approximately the same size are used. The object is to compare quantitatively the physiological effect of a known quantity of a standard preparation with a known amount of the unknown preparation on a similar animal or number of animals.

Reference Standards have been provided by the Pharmacopoeia as a basis for comparison for official assays. The following are supplied by the Food and Drug Administration of the U. S. Dept. of Agriculture, Washington, D. C.: Cod Liver Oil, standardized for vitamin A potency; Cod Liver Oil, standardized for its vitamin D potency; Ascorbic Acid; Cholic Acids; Digitalis; Epinephrine; Ergotoxine Ethanesulfonate; Estrone; Zinc-Insulin Crystals; Menadione; Nicotinic Acid; Ouabain; Posterior Pituitary; Riboflavin; Sulfanilamide; Thiamine Hydrochloride; Trypsin, etc.

Since standard preparations are not available for some substances such as parathyroid hormone and antipernicious anemia preparations, their strength is determined by the amount of material required to give a certain physiologic response.

Pharmaceutical Preparations

Pharmaceutical preparations are the prepared forms into which drugs are made for medicinal administration. Most drugs need to be

prepared in a form suitable for administration, since in their natural form they are often unsafe, distasteful, and bulky. It is therefore the task of the pharmacist, and more recently of the large pharmaceutical laboratories, to prepare drugs for administration. They endeavor to prepare the drugs in such a manner as to improve their taste, to secure their full physiological activity, and to render them safe and easy to administer. This accounts for the tinctures, extracts, ointments, etc. These preparations are made according to "official" instruction found in the U.S.P. and N.F. in order to secure uniformity in strengths and activities. Pure chemicals, such as calomel, sodium salicylate, etc., may need only to be incorporated in a tablet or pill or to be made into a solution.

It is not expected that a student of medicine be informed in the details of pharmacy; it is essential, however, that he be familiar with the preparations he prescribes.

Classes of Pharmaceutical Preparations

A. Aqueous Preparations.—These preparations have the advantage that water is a cheap and universal solvent and has no therapeutic activity. Aqueous preparations have a tendency to spoil due to bacteria.

WATERS, AQUAE, are aqueous solutions of volatile substances, usually volatile oils. Two classes are found in the U.S.P.: *Aromatic waters* are prepared either by distilling the plant or oil with water, or by triturating the oil with an adsorbent substance (talc, etc.), then extracting with water. Their doses are large. It is well to remember that the volatile substance may be thrown out when some soluble inorganic salts are added. *Waters* of the second class are prepared by passing ammonia gas into water. Their doses are small. Aromatic waters have a pleasant taste, no therapeutic properties, and are used chiefly as vehicles. The N.F. and the U.S.P. recognize numerous waters. Two of the most common U.S.P. waters are Peppermint Water and Cinnamon Water.

SOLUTIONS, LIQUORES, are aqueous solutions of nonvolatile substances made either by dissolving the pure salt directly in water, or more often by chemical decomposition. The official solutions may be administered as such, or with other aqueous preparations and water-soluble substances. The N.F. and U.S.P. recognize many solutions. Liver Solution and Epinephrine Solution are examples of U.S.P. solutions.

DECOCTIONS, DECOCTA, are solutions of vegetable principles, which are obtained by boiling parts of plants in water. They are usually 5 per cent in strength. The decoctions may be given alone or in combination with various aqueous preparations. They should always be prepared fresh. The dose of nontoxic decoctions lies between 15 and 120 cc. The U.S.P. and the N.F. recognize no decoctions.

INFUSIONS, INFUSA, are solutions obtained by soaking parts of plants in hot or cold water. They are usually of 5 per cent strength. Like decoctions, they spoil quickly, and must be prepared fresh. The dose of nontoxic infusions lies between 8 and 120 cc. The N.F. recognizes a few infusions, the U.S.P. none.

MIXTURES, MISTURAE, are liquid preparations in which substances insoluble or partly soluble in water are suspended by means of gums, and other similar substances. They usually contain sugar or syrup. The official mixtures can be combined with a wide range of drugs and preparations; alcohol, however, would have a tendency to precipitate gums. The N.F. and U.S.P. recognize few mixtures. Chalk Mixture is a U.S.P. preparation.

EMULSIONS, EMULSA, are aqueous preparations formed by suspending oils in water by means of gums or other viscid bodies. They are made by two methods. *Continental Method:* Triturate the acacia with oil, add water all at once. *English Method:* Dissolve acacia in water, add small quantities of oil and water to mucilage until all is emulsified. Four parts oil, 2 parts water, 1 part acacia forms the nucleus of all cod-liver oil emulsions. Emulsions usually should be administered alone; certain drugs, however, such as medicated syrups and various water-soluble drugs, may be administered with them. Since they naturally contain acacia, alcohol should not be added, as alcohol precipitates gum and will destroy the emulsion. The U.S.P. and N.F. recognize but few emulsions. Examples: Cod Liver Oil Emulsion, U.S.P.; and Turpentine Oil Emulsion, N.F.

MUCILAGES, MUCILAGINES, are aqueous solutions of gums, starches, or other colloid-like bodies. They are made by either the hot or cold process: the former being solution by heat, the latter by percolation. They are used as vehicles and demulcents. The mucilages are suitable for water-soluble substances, and, owing to their viscosity, are frequently used in the preparations of emulsions and suspensions. Few mucilages are official. There are two U.S.P. mucilages, Acacia Mucilage and Tragacanth Mucilage.

SYRUPS, SYRUPI, are concentrated solutions of sugar and water with or without the addition of active medicaments. Syrups are usually prepared by first making an infusion, either by heat or by percolation, and then adding sugar. In special cases modifications may be introduced. Some syrups are prepared by mixing a fluidextract with simple syrup. Syrups are used as vehicles, preservatives, and as sweetening agents. The dose of flavoring syrups is practically unlimited. The N.F. and U.S.P. recognize a large number of syrups. Two common U.S.P. syrups are Citric Acid Syrup and Orange Syrup.

LOTIONS, LOTIONES, are aqueous liquid preparations (solutions or mixtures) intended for local applications without friction or rubbing. Two common N.F. lotions are Phenolated Calamine Lotion and White Lotion. The U.S.P. recognizes Calamine Lotion.

MAGMAS, MAGMATA, are aqueous suspensions of insoluble or nearly insoluble substances. The N.F. and U.S.P. recognize few magmas. The U.S.P. recognizes Magnesia Magma.

B. Alcoholic Preparations.—Alcohol acts as a solvent for volatile oils, resins, and alkaloids. Alcohol is a good preservative. The pharmacological action and its incompatibility with aqueous solutions (gums, albumin, and some inorganic salts) must be kept in mind in prescribing these preparations.

SPIRITS, SPIRITUS, are alcoholic solutions of either gaseous, liquid, or solid volatile bodies. They are prepared by simple or chemical solution or by distillation. While there is no uniform strength for spirits, they are usually about 5 to 10 per cent. The spirits are generally not used as such, but are added to other preparations as flavoring agents. The volatile substance is thrown out of solution by water in most of the official spirits except those of nitrous ether and ammonia. Their dosage is 1 to 2 cc. The N.F. and U.S.P. each recognize about a dozen spirits. Two common U.S.P. spirits are Peppermint Spirit and Aromatic Ammonia Spirit.

ELIXIRS, ELIXIRIA, are sweetened alcoholic aromatic preparations often containing small amounts of medicinal substances. There are two classes: (1) pleasant elixirs, such as aromatic elixir and elixir of glycyrrhiza; and (2) medicated elixirs, containing one or more active ingredients. The former are used as flavoring vehicles. The medicated

elixirs are usually used alone for the administration of organic and inorganic salts, including the alkaloids. Their alcohol content is about 25 per cent. The N.F. recognizes a large number of elixirs. Aromatic Elixir and Phenobarbital Elixir are U.S.P. preparations.

TINCTURES, TINCTURAE, are alcoholic solutions of nonvolatile substances (exception, tincture of iodine). The strength of tinctures varies. They are very useful preparations. Since they usually contain tannic acid, they generally cannot be used with agents incompatible with tannic acid. Those tinctures containing resinous materials or oils will usually precipitate with water. Tinctures of potent drugs are usually 10 per cent in strength, tinctures of fresh drugs 50 per cent, while most of the others are 20 per cent, although some tinctures contain only 0.4 per cent of active drug. The dose is quite uniform, being about 2 to 4 cc. of the nontoxic preparations. They are often suitable for administration in their original form. Many may be diluted with water, but some may precipitate on dilution with water. A large number of tinctures are found in the U.S.P. and N.F. Typical U.S.P. tinctures include Digitalis Tincture and Aromatic Rhubarb Tincture.

FLUIDEXTRACTS, FLUIDEXTRACTA, are liquid alcoholic extracts representing exact strength of drugs, i.e., 1 cc. containing the medicinal properties of 1 gram of the crude drug. They are usually prepared by percolation. Fluidextracts may be considered concentrated tinctures. The advantages of fluidextracts over tinctures and other preparations are (1) they possess the same strength as that of the drug from which they are derived. (The dose of the drug is therefore the same as the dose of the fluidextract); (2) they keep well, being made with alcoholic menstrua; (3) they are concentrated, a very small quantity being required for the administration of a therapeutic dose.

The fluidextracts are an important group of remedies. They are very similar as a group: their strength is identical; their manufacture quite similar; their medicinal properties are those of the drug from which they are manufactured. They are best diluted with some tincture or elixir. They may be incorporated with other ingredients to make pills, tablets, suppositories, etc. The N.F. recognizes a large number and the U.S.P. approximately a dozen fluidextracts. Ergot Fluidextract and Glycyrrhiza Fluidextract are typical U.S.P. preparations.

ALCOHOL, ALCOHOL. Various ethyl alcohol preparations are official. Alcohol (95% by volume) U.S.P.; Diluted Alcohol (49% by volume) U.S.P. are examples.

C. Other Fluid Preparations.—

GLYCERITES, GLYCERITA, are solutions of medicinal substances in glycerin, a substance devoid of pharmacological action. Most glycerites are solutions, but the glycerite of starch is a semisolid. They are permanent preparations and are intended for local application. The glycerite of starch is often used as an excipient in making pills. A few glycerites are recognized by the N.F. and U.S.P. Starch Glycerite and Glycerite Boroglycerin are typical U.S.P. glycerites.

LINIMENTS, LINIMENTA, are preparations of irritant drugs in oily, soapy, or alcoholic vehicles and are intended to be applied to the skin by friction. They are usually volatile, soapy, or oily to provide lubricant properties for the application by friction. Some contain insoluble matter, some are clear alcoholic solutions, and some are opaque. Since some are alcoholic solutions (soap liniment), and some are oleaginous solutions (camphor liniment), while one is a transparent semisolid mass (turpentine liniment) there seems to be no definite class into which liniments can be placed, hence they are placed under

"other fluid preparations." Several liniments are found in the N.F. and a few in the U.S.P. Two common U.S.P. liniments are Camphor Liniment and Soft Soap Liniment.

FIXED OILS, OLEA PINGUA, are neutral esters of vegetable or animal derivatives, being compounds of acids (chiefly oleic, palmitic, and stearic) with glycerin. Combinations of varying proportions of olein (glyceryl oleate), palmitin (glyceryl palmitate), and stearin (glyceryl stearate) form the fixed oils common in oils and fats. The larger the proportion of olein, the more liquid is the substance, and as the stearin increases the more solid is the preparation. Fats split into glycerin and the fatty acids. The tendency to decomposition with the production of a disagreeable odor is termed *rancidity*. The N.F. recognizes few fixed oils. A large number of fixed oils are found in the U.S.P., among which are Olive Oil and Cod Liver Oil.

VOLATILE OR ESSENTIAL OILS, OLEA VOLATILA, are volatile, odoriferous liquids derived from plants. They may contain, or consist of, neutral principles, aldehydes, ketones, phenols, esters, or compound ethers. They are separated from the plant by several methods, such as distillation with water, distillation with steam, destructive distillation, vacuum distillation, expression, enfleurage, and by percolation. These oils are chiefly used in the form of aromatic waters and spirits, as flavoring agents. The N.F. recognizes about a dozen volatile or essential oils. There are many U.S.P. volatile oils. Common U.S.P. volatile oils are Spearmint Oil and Peppermint Oil.

OLEORESINS, OLEORESINAE, are thick liquid preparations consisting of volatile oils and resins extracted from vegetable substances by ether, acetone or alcohol. There are two classes of oleoresins: (1) The natural oleoresins, such as turpentine and copaiba, which are mixtures of volatile oil and resin which come from plants. (2) The pharmaceutical oleoresins which are prepared from drugs which contain the volatile oil and resin, such as oleoresin of gentian or oleoresin of cinchona. They may be administered in the form of emulsions, pills, suppositories, ointments, or be placed in capsules. The N.F. recognizes few oleoresins. There is one U.S.P. oleoresin, Aspidium Oleoresin.

SPRAYS, NEBULAE, are solutions intended for the application of medicaments in solution to the throat and nose by means of suitable atomizers. They consist largely of light petrolatum or physiological saline into which are dissolved various aromatics and other medicaments. The N.F. recognizes Ephedrine spray and Compound Ephedrine spray.

HONEYS, MELLITA, are sweet liquids having honey as a base. They were at one time used frequently as vehicles.

AMPULES, AMPULLAE, are hermetically sealed containers, commonly glass, containing medicinal substances in sterile solution (usually aqueous) intended as a rule for parenteral use. Ampules of iodine, however, are offered for topical application. Wax ampules of silver nitrate are prepared for instillation of silver nitrate in the eyes of newborn babies, and there are thin glass ampules of amyl nitrate to be crushed in a cloth and inhaled. They may contain dry chemicals, solutions, or suspensions in oil but most often they contain aqueous solutions. The label must state plainly the amount of active medicinal ingredients in a stated unit of solution. The glass should be insoluble in water so as not to turn the solution alkaline on long standing. The N.F. recognizes a large number of ampules, including Calcium Chloride Ampules.

INJECTIONS, INJECTIONES, are solutions and suspensions of drugs indicated for parenteral administration. The vehicles are aqueous or

oils. Injections are prepared, placed in suitable containers, sealed, and sterilized. Nontoxic and harmless preservatives may be added to insure permanency or usefulness to the products. The following injections are among those included in the U.S.P.: Bismuth Subsalicylate Injection, Caffeine and Sodium Benzoate Injection, Dextrose Injection, Digitalis Injection, and others.

VINEGARS, ACETA, are medicated substances in vinegar or diluted acetic acid. The vinegars may be prescribed in aqueous, syrupy, or mildly alcoholic vehicles. The N.F. contains Squill Vinegar.

COLLODIONS, COLLODIA, are solutions of guncotton and ether, alcohol, or acetone. There are two U.S.P. preparations: Collodion and Flexible Collodion.

D. Solid or Semisolid Preparations.—

EXTRACTS, EXTRACTA, are solid or semisolid preparations obtained by evaporation of solutions of medicinal principles of drugs. The menstruum employed is varied, being alcoholic, hydro-alcoholic, aqueous, alcoholic and alkaline, or alcoholic and acid. The percentage of extract to drug varies from 200 (extract of opium) to 800 (extract of bile). Most extracts are potent and are convenient for administration in the form of pills, ointments, etc. They may require dilution, as they are usually quite active. Since they are usually used in solid preparations, incompatibilities rarely arise. The N.F. and U.S.P. each recognize about a dozen extracts. Two U.S.P. extracts are Belladonna Extract and Glycyrrhiza Extract.

PILLS, PILULAE, are spherical or elongated masses of medicinal substances in sizes from 0.1 to 0.3 gram. Various solid and semisolid, and some fluid, official drugs and preparations may be prescribed as pills. The manufacture of pills by the pharmacist, while formerly an important task, is becoming a lost art, due to the introduction of machinery. The N.F. recognizes several pills. The U.S.P. recognizes Hexylresorcinol Pills.

MASSES, MASSAE, are soft masses of medicinal substances capable of being made into pills. The manufacture of the official masses is a matter of little difficulty, as in each prescription the amount of liquid is sufficient to make a mass of the required consistency. Masses are not important U.S.P. or N.F. preparations. Ferrous Carbonate Mass is an N.F. preparation.

SUPPOSITORIES, SUPPOSITORIA, are suitable masses of medicated substances, usually in oil of theobroma, glycerinated gelatin, or glycerin, intended for insertion in the rectum, urethra, or vagina. The base melts at body temperatures. The U.S.P. gives general formulas for manufacture of suppositories with oil of theobroma and with glycerinated gelatin. Suppositories are not important official preparations. The U.S.P. recognizes Glycerin Suppositories.

TROCHES, TROCHISCI, are small flattened masses of active medicinal substances, usually powders, incorporated in sugar and gum; they are intended to be administered by slowly dissolving in the mouth. They are suitable for the administration of medicines intended for application to the throat, and for the administration of fairly mild and tasteless medicines in a palatable form. Troches are manufactured by massing and by compression. They are usually demulcent or astringent in action. The U.S.P. recognizes Penicillin Troches.

TABLETS, TABELLAE, are small disks of medicated powders. There are three common kinds of tablets. *Compressed tablets* are formed by high compression, using the pure drug with no excipient added. Such drugs as acetyl-salicylic acid, acetophenetidin and barbital are

usually administered in this form. They are used similarly to pills. The commercial tablets may vary considerably in size, but usually are quite large. The N.F. and U.S.P. recognize numerous tablets.

Hypodermic tablets are small and consist of medicinal substances blended with some substance known to be completely soluble and inert. They are administered by injection after dissolving in 1 or 2 cc. of water. Quick solubility and dose accuracy are prime requisites in their manufacture. Only relatively very active drugs are made up into hypodermic tablets, e.g., atropine, nitroglycerin, strychnine, and morphine. Aseptic conditions must be maintained at all stages in their manufacture and administration.

Tablet triturates are small tablets of active drugs, such as morphine sulfate, atropine, and calomel. They usually weigh about 1 grain and may contain some diluent such as lactose or sucrose.

POULTICES, CATAPLASMA, are pasty preparations for external application, usually employed to reduce inflammation or to act as counter-irritants. They are generally devoid of medicinal properties. Linum (flaxseed), ground flaxseed, is used extensively for making poultices. Poultices are not important N.F. and U.S.P. preparations.

CERATES, CERATA, are combinations of medicinal substances with fats and waxes intended to be used by spreading on cloth or paper. The preparations are similar to ointments but rendered harder by the addition of wax. They are applied as one would apply a plaster. Ceratum (simple cerate) provides an excellent basis for the preparation of other cerates. Few cerates are official. The U.S.P. has deleted all cerate preparations, but the N.F. still retains them as a class distinct from ointments.

OLEATES, OLEATA, are combinations of alkalies of metallic oxides or alkaloids with oleic acid. Like ointments, they produce the therapeutic effect of the active ingredient through absorption of the latter on application to the skin by inunction. Oleates are preparations of little importance. The U.S.P. recognizes Mercury Oleate.

RESINS, RESINAE, are those plant products, soluble in alcohol and insoluble in water, obtained either as the residue from the distillation of an oleoresin, or by pouring a concentrated alcohol extract into water. The resins are best given in the form of pills or suppositories. Their taste is usually disagreeable and not readily disguised in fluid preparations. There are few official resin preparations.

PLASTERS, EMPLASTRA, are solid or semisolid preparations containing medicinal substances intended to be applied to the skin, and of sufficient adhesiveness to adhere firmly. Commonly used plaster bases are gum resins, lead plaster, resin plaster, isinglass, and India rubber. Plasters possess higher melting points than ointments and oleates, and are not intended to melt at body temperature. They act as supports or counter-irritants. Few plasters are official. Mustard Plaster and Adhesive Plaster are typical U.S.P. plasters.

At present machine-made plasters with rubber bases have practically replaced the old-fashioned type of plasters; the pharmacist is rarely called upon to spread a plaster.

OINTMENTS, UNGUENTA, are soapy, oily substances which are applied to the skin by inunction. They consist of active medicaments combined with a base, such as wool fat, lard, white petrolatum, ointment of rose water, and benzoinated lard. Wool fat is supposed to be the base most quickly absorbed by the skin, lard comes next, while petrolatum is slowly absorbed. Hydrogenated oils have been suggested as useful

ointment bases. More recently triethanolamine, cetyl alcohol, glyceryl, monostearate and bentonite have been used in the preparation of various ointments.

Anhydrous and hydrophylic ointment bases are now in use. Penicillin Ointment, U.S.P. uses an anhydrous ointment base.

POWDERS, PULVERES, are finely powdered drugs for external or internal use. Powdered drugs may be combined as such and prescribed in capsules or cachets for internal use, or they may be ordered mixed with water or taken in the dry form. They are usually made by trituration with mortar and pestle, or by mixing the ingredients, already reduced to a fine powder, with a spatula on a large piece of paper. Most of the official powders are mixtures of several active drugs. Compound Effervescent Powder is the only U.S.P. powder.

TRITURATIONS, TRITURATIONES, are powders obtained by triturating the active drug, usually with lactose. The U.S.P. gives a general formula calling for 10 per cent of the drug and 90 per cent of lactose. They furnish a convenient means of administering active solid drugs which can be reduced to a fine powder. Neither the N.F. nor the U.S.P. recognizes any triturations.

CAPSULES, CAPSULAE, are shells of gelatin used for the administration of solids, masses, and liquids. The U.S.P. and N.F. contain several: Digitalis Capsule, U.S.P., Castor Oil Capsule, N.F.

References

Arny, H. V.: Principles of Pharmacy, ed. 4, Philadelphia, 1937, W. B. Saunders Co.

Bethea, O. W.: Materia Medica, Drug Administration and Prescription Writing, ed. 5, Philadelphia, 1938, F. A. Davis Co.

British Pharmacopoeia, London, 1932, and Addendum, 1941. The General Council of Medical Education and Registration of the United Kingdom.

Burns, J. H.: Biological Standardization, New York, 1937, Oxford University Press.

Caspari, C. C.: A Treatise on Pharmacy, ed. 7, Philadelphia, 1926, Lea and Febiger.

Cook, E. Fullerton, and LaWall, C. H.: Remington's Practice of Pharmacy, ed. 8, Philadelphia, and London, 1936, J. B. Lippincott Co.

Epitome of the U.S.P. and N.F. American Medical Association, Chicago, 1947.

Edmunds, C. W., and Cushny, A. R.: Laboratory Guide in Experimental Pharmacology, Ann Arbor, Mich., 1939, George Wahr.

Fuller, H. C.: The Story of Drugs, New York, 1922, D. Appleton-Century Co.

Husa, Wm. J.: Pharmaceutical Dispensing, ed. 2, Easton, Pa., 1941, Mack Printing Co.

Jackson, D. E.: Experimental Pharmacology and Materia Medica, ed. 2, St. Louis, 1939, The C. V. Mosby Co.

LaWall, C. H.: Four Thousand Years of Pharmacy, Philadelphia, 1926, J. B. Lippincott Co.

Lazar, Charles: Manual of Cosmetics, Cleveland, 1938, The Sherwood Press.

Lyman, R. A.: American Pharmacy, Philadelphia, 1945, J. B. Lippincott Co.

Munch, J. C.: Bio-assays: A Handbook of Quantitative Pharmacology, Baltimore, 1931, William Wood & Co.

New and Nonofficial Remedies, Chicago, 1947, American Medical Association.

Scoville, W. L.: The Art of Compounding, ed. 5, Philadelphia, 1927, P. Blakiston's Son & Co. Revised by H. H. Powers, 1943.

The National Formulary, ed. 8, 1947.

The United States Pharmacopoeia XIII, 1947.

United States Dispensatory, ed. 24, Philadelphia, 1947, J. B. Lippincott Co.

Youngken, H. W.: Textbook of Pharmacognosy, ed. 5, Philadelphia, 1943, The Blakiston Co.

CHAPTER III

PRESCRIPTION WRITING

"The prescription is the keystone to the entire arch of therapeutic endeavor. It rests on the diagnosis and prognosis of the case, on the one side, and the physician's knowledge of pharmacology and therapeutics on the other. Any weakness on either side of the arch reflects itself in the setting of the keystone."—Bernard Fantus.

THE PRESCRIPTION

Unfortunately, prescription writing has been neglected both in medical school curricula and medical practice. The pendulum seems to be swinging back to where teachers, students, and physicians are again seeing the practical value of being able to incorporate into a prescription the physician's diagnosis, prognosis, and knowledge of the patient's illness.

A prescription (Latin *prae* and *scribo,* means literally *written before*) is an order for medicine sent by a physician to a pharmacist. The modern tendency in prescribing drugs is to make prescriptions simple. Instead of prescribing a hopeful mixture of numerous drugs of questionable value the prescription of a single drug with definite and specific actions is desired. *The simplest prescription is usually the best.* A typical classical prescription consists of the following:

1. Name of patient and address.
2. Date.
3. Superscription: ℞ is the abbreviation for the Latin word *recipe,* take thou.
4. Inscription: the ingredients and their amounts.
   Basis: the principal substance.
   Adjuvant: the substance used to aid the action of principal substance. (Seldom used.)
   Corrective: modifying or correcting action of principal substance. (Seldom used.)
   Vehicle: an agent in which the drugs are incorporated.
5. Subscription: directions to the pharmacist.
6. Signature: directions to patient; this should be written in English.
7. The physician's signature.

The following illustrates a complete prescription.

Name		Mrs. L. O. Rambo,
Address		1499 Hythe St.,
		St. Paul, Minn.
Date		March 31, 1948.
Superscription	℞	
Inscription:		
	Basis	Chloral Hydrate ---------- 4.00 Gm.
	Adjuvant	Sodium Bromide ---------- 2.00 Gm.
	Corrective	Orange Syrup ---------- 45.00 cc.
	Vehicle	Distilled Water ---------- 30.00 cc.
Subscription		M.
Signature		Sig.: One teaspoonful as directed.
Physician's signature		Frank B. Astroth, M.D.
		Medical Arts Building,
		St. Paul, Minn.

Name of the Patient and the Address.—The name and address of the patient should be written distinctly in the prescription, as it is necessary for the pharmacist to place it on the label. This is important if there is more than one patient in the family. If the patient is a child the name should be followed by information as to age, written always by figure and months and years as, e.g., Mary Brown (4 yr.). The name may sometimes be omitted from a prescription for venereal diseases, or it may be still wiser to use initials and age data. Some state laws require the full name on all prescriptions.

Date.—The physician should place the date on the upper part of the prescription sheet, preferably after the patient's address. The date on the original copy should prove of value in case of legal complications, and the date on the duplicate copy often proves of value to the prescriber.

The present Federal Anti-narcotic Law requires that the date be entered by the prescriber. The pharmacist generally uses the lower left-hand corner for entering the narcotic registry number, date, etc.

Superscription

The word superscription comes from the Latin word *superscribo* "to write on top." The superscription consists of the symbol ℞, which is the abbreviation for the Latin word *recipe* (pronounced rāy-kip-a), which means "take" (thou). It is a command, and has as its object the quantities of the drugs mentioned in the inscription. The object in most prescriptions will be the quantity of the drugs mentioned in the inscription, e.g., gr. ij. The oblique dash across the final stroke of the ℞ probably is derived from the astronomical sign ♃ which was used as a prayer to Jupiter to bless the remedies. The oblique line may have been used by the Romans much as we now use the period.

Inscription

The word inscription from the Latin *inscribo,* means "to write upon" or "within." It contains the object of the command "take thou" and is composed of the official names of the drugs which are used, along with solvents, flavoring vehicles, etc. Some prescriptions may contain the various parts of the inscription as shown in the above example. In this example the chloral hydrate is the basis or principal drug. The sodium bromide aids the action of the principal drug and may be considered the adjuvant. Orange syrup modifies or corrects the action or taste of the principal drug and adjuvant. The water dissolves and dilutes the drugs used in the prescription.

The lines of demarcation between the various parts of the inscription are not always clearly drawn. For instance, the adjuvant drug may have action as important as the principal drug. The corrective may possess modifying and corrective values and may also dissolve and dilute the principal ingredients and thus eliminate the necessity of using a vehicle such as water. A competent prescriber lists the ingredients in the order in which they are compounded. It is usually best to put the important ingredients first, with the vehicle or diluent last.

Capitalization.—Capitals are used for the important words of all official titles. Prepositions and conjunctions are not capitalized.

Abbreviations.—The following abbreviations are found in the inscription:

Q.R. *(quantum rectum)* meaning the "quantity is correct" when written after the dose. This indicates to the pharmacist that the amount prescribed is intentional. To illustrate:

℞

Digitalis Tincture ---------- f3iv (Q.R.)

Another method commonly used to indicate that the dose prescribed is correct is to follow the symbol or abbreviation of the quantity and its numerals by parentheses enclosing the English name of the quantity and numeral, thus:

℞

Morphine Sulfate ---------- gr.iij (three grains)

A heavy line underscoring a quantity has the same meaning as Q.R. Example:

℞

Morphine Sulfate ---------- gr. iv

Q.S. *(quantum sufficit)*, the Latin for "as much as suffices," may be placed after the vehicle to indicate that the pharmacist is expected to use his judgment as to the amount of the substance needed. It is usually placed after the vehicle or excipient, which is ordinarily the last item of the prescription. To illustrate:

℞

Potassium Bromide ---------- 2.0 Gm.
Aromatic Elixir ----------q.s. 60.0 cc.

Ad means "to" or "up to" and is used after the name of the vehicle. It is often used after q.s., as q.s. ad. To illustrate:

℞

Potassium Permanganate ---------- f3vj
Distilled Water ----------q.s. ad gr. xxx

Ss, the abbreviation of *semis* or *semissem* meaning "one-half" may be employed following a symbol or abbreviation. To illustrate:

℞

Ammonium Bromide ---------- 3ss

means "take thou one-half dram of ammonium bromide."

Aa, the abbreviation of *ana*, meaning "of each" may be employed following two or more ingredients of a prescription to indicate that equal amounts of each are to be taken. Example:

℞

Ammonium Bromide
Potassium Bromide ----------āā 5.0 Gm.

Abbreviations and symbols are used in specifying quantities, and each symbol or abbreviation is followed by Roman numerals. In writing numerals, the final *i* is written as *j* to prevent errors, such as taking the *ii* for a v. Dots are placed above the numerals *i* and *j* to aid the pharmacist in interpreting the numerals. For example, eight ounces are written ȝviij.

Subscription

The subscription is the subscriber's direction to the pharmacist. Formerly directions were quite elaborate, but now they are brief, allowing the pharmacist to use his own judgment as to the best means of compounding the remedy. The directions usually consist of short statements, such as "Divide into 10 pills," "Mix and place in 10 capsules," or the subscription may be only one word "Mix."

The pharmacist should place the name of the patient on the bottle or container exactly as the doctor has written it on the prescription.

Signature.—The signa (signature), meaning "write," follows the subscription. The abbreviation *S.* or *Sig.* is usually used. The signature consists of the directions to be copied on the label for the instruction of the patient. These directions should be written briefly and plainly in English and should be of such a nature as to guide the patient in the safe and proper use of the drug.

The direction *as directed* should rarely be used and is justified only when there is no danger of improper use. Where a medicine is not to be administered by mouth, or in case of poison, the signa may be written as follows:

Sig.—"Not to be taken." Use to moisten dressing.
Sig.—"Poison—not to be taken." Apply externally.
Sig.—"Poison." Apply externally with massage.

The pharmacist may carry separate labels bearing the words "Poison," "Not to be taken," etc., but as these may be detached, it is more desirable to have the pharmacist use a prescription label carrying the printing desired on its face.

Physician's Name.—The full name of the physician should be placed at the bottom of the prescription. When the prescriber uses his own private blanks carrying his name and address, he can naturally take more liberties than when such is not the case.

Additional Instructions for Prescription Writing.—

"Shake well" should be placed on bottles containing mixtures or suspensions of insoluble matter.

Non rep., the abbreviation for *non repetatur*, meaning "do not repeat," should be placed anywhere on the prescription when the prescription is not to be refilled.

Pp., for *pauperissimus*, meaning "very poor," should be placed at the top of the prescription, or near the patient's name, when the patient is poor and the physician desires to invite the pharmacist to charge a low price for the medicine.

Latin Grammar in Prescription Writing

There is a difference of opinion concerning the advisability of using Latin in prescription writing. Some teachers favor the use of Latin, but many are now avoiding its use and are teaching the writing of prescriptions in English. The trend toward the use of English is well illustrated by the use of English in the primary titles and Latin in secondary titles in the 1947 editions of the United States Pharmacopeia, the National Formulary, and the New and Nonofficial Remedies.

The following pages on prescription Latin are given for those who prefer to prescribe in Latin. Actually no great expenditure of time need be required to become proficient in the art of writing prescriptions in Latin. The student need only learn the Latin official names of the drugs, the necessary changes in terminations (usually genitive), and a few Latin words or phrases commonly used in the inscription.

Prescription Latin.—Latin has no article; the declension of nouns is accomplished by changing their terminations. Latin has the following cases: nominative, genitive, dative, accusative, ablative, and vocative. Since the dative, accusative, and vocative are rarely used in the writing of prescriptions, and the ablative only occasionally,

only the genitive will be mentioned to any great extent here. The genitive of Latin corresponds to the possessive of English. The following rules for the formation of the genitive case are useful:

RULE 1.—*First Declension.*—All nouns ending in **-a** or **-e** (**-e** from the Greek) form the genitive in **-ae**. All are of feminine gender. Examples: *aqua*, gen., *aquae*.

CASE	SINGULAR	PLURAL
Nom.	aqua **-a (e)** a water	aquae **-ae**
Gen.	aquae **-ae (es)** of a water	aquarum **-arum**
Acc.	aquam **-am (en)** a water	aquas **-as**
Abl.	aqua **-a (e)** with, by or from a water	aquis **-is**

Exceptions: Aspidosperma, physostigma, and theobroma form the genitive in **-atis**, and *folia*, which is nominative plural, forms the genitive *foliorum*.

RULE 2.—*Second Declension.*—Masculine nouns in the nominative singular end in **-us**, **-er**, and **-os**, the neuter in **-um**, and **-on**, and they form the genitive in **-i** as in *conium—conii*.

CASE	SINGULAR			PLURAL	
Nouns in	**-us**	**-um**	**-on**	**-us**	**-um** and **-on**
Nom.	**-us**	**-um**	**-on**	**-i**	**-a**
Gen.	**-i**	**-i**	**-i**	**-orum**	**-orum**
Acc.	**-um**	**-um**	**-on**	**-os**	**-a**
Abl.	**-o**	**-o**	**-o**	**-is**	**-is**

Exceptions: Rhus, genitive *rhois; flos*, genitive *floris; limon*, genitive *limonis; fructus, cormus, quercus*, and *spiritus* do not change.

RULE 3.—*Third, Fourth, and Fifth Declensions.*—There is considerable variation in the formation of the third declension. Few nouns of the fourth and fifth declensions are found in medicine. *In general, all* nouns other than those of the first and second declensions, regardless of terminations, form the genitive in **-s** and **-is**. Example: *Elixir*, genitive *elixiris*.

Some lengthen in the terminations:

-as, genitive **-atis**; as *acetas, acetatis*
-is, genitive **-idis**; as *anthemis, anthemidis*
-o, genitive **-onis**; as *persio, persionis*
-x, genitive **-icis**; as *cortex, corticis*

Exceptions: Mas, genitive *maris; phosphis, sulfis*, etc., genitive **-itis**; *mucilago*, genitive *mucilaginis; pulvis*, genitive *pulveris; fel*, genitive *fellis*.

The following words do not change in their genitive: buchu, cannabis, catechu, digitalis, hydrastis, condurango, cusso, fructus, jaborandi, kino, matico, sassafras, sago, sinapis, spiritus, gambir, sumbul. Amyl is unchanged or changed to amylis.

Note: More than three-fourths of all official names are included in the first and second declensions.

Adjectives agree in number, gender, and case with the nouns they modify. They are declined as are nouns, and belong to either the first, second, or third declension. Latin nouns may have but one gender but every adjective must have all three genders so that it may modify the nouns of any gender. Thus we say: Syrupus albus, not syrupus alba, nor syrupus album. Tinctura aromatica, not tincturae aromaticus or tinctura aromaticum.

Adjectives may be formed from nouns or other adjectives by adding -atus or -osus to the main part of the word. Adjectives ending in -atus—

MASC.	FEM.	NEUT.
Activatus	-a	-um activated
Ammoniatus	-a	-um ammoniated
Benzoinatus	-a	-um benzoinated
Hydratus	-a	-um hydrated
Praecipitatus	-a	-um precipitated

Verbs.—Verb forms do not appear in the titles of chemicals or pharmaceutical preparations and have a limited use in the subscriptions and signas of prescriptions. The present tendency is to write the signa in English, therefore little time need be spent on verbs.

Adverbs are seldom used in prescriptions. The two most frequently used are—*bene*, meaning well; *statim*, meaning immediately.

Conjunctions.—The most common conjunctions used in prescription writing are *vel* meaning or; *et*, meaning and. Their construction is the same as in English.

Prepositions.—Latin prepositions are accompanied by a modification of the case of the nouns which they govern. The following prepositions govern the accusative: *ad* (up to, to); *ante* (before); *in* (into); *post* (after); *secondum* (according to).

The following prepositions govern the ablative case: *cum* (with); *in* (in); *pro* (for, according to); *sine* (without). *Ana* (of each) is governed by the *genitive* case.

Latin Names

In writing the Latin titles of preparations of drugs the class to which they belong is written first, as extractum, tinctura, etc. The name of the drug or drugs comes next, as Cardamom in Tinctura Cardamomi. The qualifying adjective, if there is one, comes last. Example: Tinctura Cardamomi Composita.

In writing the titles of chemical compounds which form more than a single compound, the adjective used to distinguish them is written after the principal words. Example: Hydrargyri Iodidum Flavum.

If a title consists of a noun and an adjective, the noun in the nominative precedes the adjective which must agree with the noun in gender and number. Example: Ferrum Reductum, Acidum Hydrochloricum, Acidum Hydrochloricum Dilutum.

When a Latin title contains two nouns connected by the conjunction et, **both nouns are in the same case. Examples: Potassii et Sodii Tartras, Quininae et Ureae Hydrochloridum.**

Rules for the Formation of Latin Nouns

A few rules showing how the Latin names may be formed from the English words will be of great assistance to the student of prescription writing. Most Latin names of drugs are merely Latinized English words.

Alkaloids.—Alkaloids, and a few synthetic organic medicinals which have English names ending in -ine are Latinized by changing the -ine to -ina. Example: Quinine (English), Quinina (Latin nom.), Quininae (Latin gen.).

Apomorphine, atropine, caffeine, epinephrine, morphine, physostigmine, scopolamine, etc., are a few common alkaloids which follow this

rule. Aminopyrine, antipyrine, arsphenamine, and chloramine are synthetic medicinals which also follow this rule.

Acids.—English names of acids may be Latinized by changing the English ending -ic to -icum, and -ous to -osum. Examples: Hydrochloric acid (English), Acidum Hydrochloricum (Latin nom.), Acidi Hydrochlorici (Latin gen.); Nitrous acid (English), Acidum Nitrosum (Latin nom.), Acidi Nitrosi (Latin gen.).

Acid Radicals.—If the English name ends in -ate the Latin nominative ends in -as and the Latin genitive in -atis. Example: Sulfate (English), Sulfas and Sulfatis (Latin nom. and gen.). If the English name ends in -ite the Latin nominative is -is, and genitive -itis. Examples: Sulfite, Sulfis, Sulfitis. If the English word ends in -ide the Latin nominative is formed by changing the final e to -um and the genitive by changing the -um to -i. Example: Bromide (English), Bromidum (Latin nom.), Bromidi (Latin gen.).

Glucosides, Resinoids, Etc.—The Latin and the English names of these substances are the same except that the Latin name is formed by adding -um to the English for the nominative and changes the -um to -i to form the genitive. Example: Strophanthin (English), Strophanthinum (Latin nom.), Strophanthini (Latin gen.).

Many words ending in -in and -ine are Latinized by changing to -inum. Examples: Acetophenetidin (English), Acetophenetidinum (Latin nom.), Acetophenetidini (Latin gen.). Carmine (English), Carminum (Latin nom.), Carmini (Latin gen.).

Other words coming under this rule are: Albumin, Albuminum; Aloin, Aloinum; Antitoxin, Antitoxinum; Glycerin, Glycerinum; Benzoin, Benzoinum; Phenolphthalein, Phenolphthaleinum; Toxin, Toxinum.

Some words ending in -en or -ene form the Latin by becoming -enum. Examples: Cinchophen—Cinchophenum—Cinchopheni. Ethylene—Aethylenum—Aethyleni. Additional examples are: Merbaphen, Merbaphenum; Neocinchophen, Neocinchophenum; Naphthalene, Naphthalenum; Tetrachlorethylene, Tetrachlorethylenum.

Metals.—The Latin name of metals is the same as English except in the case of a few of the ancient metals. Examples: Sodium (English), Sodium (Latin nom.), Sodii (Latin gen.).

Other Drugs.—The English name is made the Latin name if suitable, e.g., cinchona, opium, colchicum, hyoscyamus, etc.

When the English ends in -ol the Latin nominative is the same, and the Latin genitive is formed by adding -is Example: Phenol (English), Phenol (Latin nom.), Phenolis (Latin gen.).

Latin Phrases and Abbreviations

Latin phrases and abbreviations which occur frequently in prescriptions should be known. Some are a traditional part of prescription writing and usually are employed in the directions to the pharmacist or patient even though the rest of the prescription is written in English. The pharmacist transcribes the directions to the patient, however, in English. The following words and phrases are commonly used:

ad libitum (ad lib.)	at pleasure; freely; as much as wanted
ana (aa or āā)	of each
ante (ā)	before
ante cibum (a.c.)	before meals

aqua	water
aqua destillata	distilled water
bis in die (b.i.d.)	twice daily
capsula (cap.)	capsule
chartula	powder
cum (c̄)	with
dividatur in partes aequales (d. in p. aeq)	let it be divided into equal parts
fac; fiat; fiant (f; ft.)	make; let be made; let them be made
fac tales doses No. XX	make twenty such doses
gutta; guttae (gtt.)	a drop; drops
hora (h.)	hour
misce (M.)	mix
misce et divide in	mix and divide into
misce et fac solutionem	mix and make a solution
misce et pone in	mix and place into
misce et tere bene	mix and stir well
nonrepetatur (non rep.)	do not repeat
numerus (No.)	number
pauperissimus (Pp.)	pauper
pilula (pil.)	a pill
post (p)	after
post cibum (p.c.)	after meals
pro re nata (p.r.n.)	according to circumstances; occasionally
quantum satis, sufficit, or sufficiat (q.s.)	a sufficient amount; as much as is necessary
(q.s. ad)	a sufficient amount to make
quaque die (q.d.)	every day
quaque hora (q.h.)	every hour
(q. 4 h.)	every four hours
quater in die (q.i.d.)	four times a day
secundem artem (S.a.)	according to the practice
semis (ss or s̄s̄)	one-half
si opus sit (s.o.s.)	if necessary
ter in die (t.i.d.)	three times a day
tritura et fac tabellas	triturate and make tablets

STATE AND FEDERAL LAWS

Every physician should familiarize himself with the laws of his State and Country that particularly affect his profession. This applies especially to those laws pertaining to the sale of narcotic poisons, ergot, barbiturates, amphetamine, thyroid, and others.

Food, Drug and Cosmetic Act

This act was enacted into law on June 25, 1938. It prohibits the movement in interstate commerce of adulterated and misbranded food, drugs, devices, and cosmetics. It protects the public by requiring honest labeling of the nation's food, drugs, and cosmetics. The Food and Drug Administration is charged with the responsibility of enforcing this act. (For details of Act—J. A. M. A. 116: 830, 1941).

Virus, Serum and Toxin Act of 1902 provides for the maintenance of potency and purity of biologic products. Licensing power is under control of this agency. The United States Public Health Service administers this act.

Food and Drug Act of 1906 was the first extensive national food and drug law enacted by Congress. Dr. Harvey Wiley fathered the

act and even though it had many shortcomings it was an important milestone in food and drug regulatory measures.

The Caustic Poison Act of 1927 safeguards the distribution and sale of dangerous caustic substances including acids and alkalies in interstate and foreign commerce. It is enforced by the Food and Drug Administration.

The Marihuana Act of 1937 regulates the importation, manufacture, production, sale, and prescribing of marihuana. This act is enforced by the Bureau of Narcotics of the United States Treasury Department.

FEDERAL NARCOTIC REGULATIONS

The Harrison Anti-Narcotic Act was passed (March 1, 1915) for the purpose of regulating manufacture, sale, dispensing, and prescribing of narcotic drugs. The law applies to opium and coca and all of their preparations, derivatives, and salts, natural or synthetic.

CHIEF DRUGS INCLUDED UNDER THE HARRISON ANTI-NARCOTIC ACT

Opium

Opium (powdered or granulated)
Extract of Opium
Tablets of Opium
Dover's Powder
Tincture of Opium
Tincture of Dover's Powder
Magendie's Solution
Morphine Sulfate (powder, tablets, or solution)
Codeine (alkaloid, salts, tablets, or solution)
Dilaudid
Demerol Hydrochloride
Dionin
Pantopon
Apomorphine Hydrochloride
Papaverine
Stypticin

Coca

Cocaine (alkaloid, salts, tablets, or solution)
Eucaine Hydrochloride
Phenacaine Hydrochloride (Holocaine)
Tropacocaine Hydrochloride

Prescribing Narcotic Drugs.—Narcotic drugs may be prescribed only by properly licensed physicians, veterinarians, and dentists. The prescribing of narcotics requires that the date, the physician's name, registration number, and address must be written on the prescription. ***A physician must register with the Department of Internal Revenue and be assigned a number.*** Every physician should secure from the Federal Government the necessary instructions to meet the requirements of this law. The full name and address, and age of the patient must also be recorded on the prescription. The signature must be in ink or indelible pencil. Narcotic prescriptions cannot be given over the telephone. A physician is permitted to prescribe only for patients whom he attends in person. Such a prescription would appear as follows:

Frank B. Astroth, M.D.
Medical Arts Building,
St. Paul, Minn.

℞

Morphine Sulfate ---------- gr.j
Antipyrine ---------- gr.xxiv
M. ft. caps. no. vj.
Sig.: One or two a day if needed.

Frank B. Astroth, M.D.
Jan. 5, 1948

For,

Mrs. L. O. Rambo (age 38 yr.)
1499 Hythe St.,
St. Paul, Minn.

Federal Registry No. 506.

The prescription cannot be refilled. When the amount of the drug is unusual, as in treating a patient with an incurable disease, the prescription should carry an explanation.

The conditions for which narcotics may be prescribed include:

1. All acute conditions at the discretion of the physician.
2. Incurable diseases under certain restrictions.
3. The treatment of addicts, also under certain restrictions.

Certain articles are exempt and may be prescribed without reference to the narcotic rules and may be purchased without prescription. These preparations must not contain more than 0.12 Gm. (2 grains) of opium, or 0.015 Gm. (¼ grain) of morphine, or 0.06 Gm. (1 grain) of codeine or other salt or derivative of opium per ounce.

Official preparations which are therefore exempt from the provisions of the Federal Narcotic Law include:

a. Camphorated Opium Tincture, U.S.P.
b. Compound Opium and Glycyrrhiza Mixture, N.F.
c. Terpin Hydrate and Codeine Elixir, N.F.
d. Expectorant Mixture, N.F.
e. Lead and Opium Lotion, N.F., and all preparations for application on the skin, if they contain ingredients that may render them unfit for internal use.

PRACTICAL CONSTRUCTION OF PRESCRIPTIONS

The construction of a prescription may proceed as follows: After the sign ℞ write the official name of the best remedy available (basis), next the name of any drug that will aid or modify the action (adjuvant) desired. Next select the most suitable form in which to administer the medicine, whether powder, liquid, ointment, etc. Then select any substance (corrective) that may be added to render the mixture more agreeable to the patient. Then add the substance (vehicle) to dilute the active ingredients. Next decide: (1) The *amount of each ingredient* to be contained in each individual dose. (2) *Size of the single dose* (teaspoonful, tablespoonful if liquid; bulk in case of solid medication). (3) *Total bulk or volume* (size of single dose times the number of doses). Decide the number of doses to be taken in a 16-hour day. (4) Then multiply the amount of ingredients in a single dose by the total number of doses.

Reassure yourself that there are no incompatibilities or grammatical errors. Write the directions to the pharmacist and also to the patient; decide whether *non repetatur* is advisable, then check prescription.

The student can master the art of prescription writing very easily by memorizing a few general principles and by constantly applying these rules in writing useful prescriptions throughout his pharmacology and therapeutic courses.

Correct prescription writing means good therapeutics. A doctor should pride himself in building up his own armamentarium to draw from when the occasion warrants it. Simplicity in prescription writing is advisable; the art of combining drugs or of rendering a drug less disagreeable is practicing the Art of Medicine.

CLASSES OF PRESCRIPTIONS

Two large classes of prescriptions are recognized, *nonofficial* and *official*. A nonofficial prescription is a prescription written extem-

poraneously by the physician, using drugs and doses as he sees fit for the occasion. The official prescription is one which calls for a drug or mixture by name, the recipe for which is found in the U.S.P., B.P., or N.F. The following are typical examples:

Nonofficial Prescriptions.—

℞

Potassium Citrate		15.00 Gm. (ʒss)
Hyoscyamus Tincture Chloroform Water	Equal parts, up to	90.00 cc. (fʒiij)

M. Sig.: Take a teaspoonful in half a glass of water every hour until urine becomes acid or bowels move.

℞

Cod Liver Oil		90.00 cc. (fʒiij)
Peppermint Oil		q.s.
Syrup		q.s.
Acacia		q.s.
Water	q.s. ad	240.00 cc. (fʒviij)

Mix and make an emulsion.

Sig.: One dessertspoonful twice daily. (For prevention of rickets.)

Official Prescriptions.—

℞

Tincturae Iodi, U.S.P. ---------- 30.00 cc. (fʒj)

Sig.: Apply once daily as directed. (Poison Label.)

℞

Calaminae Lotionis, N.F. ---------- 180.00 cc. (fʒvj)

Sig.: Apply freely to affected parts.

Percentage Prescriptions.—When prescribing drugs for local application they may be given in percentage form as follows:

℞

Salicylic Acid		3%
Benzoic Acid		6%
Lanolin		
White Petrolatum	q.s.	30.00 Gm.

M.

Sig.: Apply locally before retiring.

Nonprescription Orders.—Pharmacists usually make a professional charge on prescriptions. If the physician wishes to avoid this charge to the patient, he may, in the case of commercial articles, write the English name of the article and the quantity, i.e. (Cod liver oil, 1 pint), but he must not sign it, for this makes it a prescription. A preparation which must be compounded extemporaneously will generally be treated as a prescription, even though the order has not been signed.

WEIGHTS AND MEASURES

The study of weights and measures is known as metrology. An accurate knowledge of the subject is necessary for the proper writing of prescriptions. Two systems of weights and measures are in use in this country: the apothecaries' and the metric. Although the metric system will ultimately be uniformly adopted, for the present it is necessary to learn both systems.

Because of certain advantages found in both systems they have been retained regardless of the repeated attempts which have been

made to adopt the metric system in this country. The U.S.P. and N.F. give dosages in the metric system.

The metric system is scientific, having been officially adopted as the method of science in most countries; and, being a decimal system similar to our monetary system, relative values of weights and measures may be readily computed by change of the decimal point. Measures in the apothecaries' system, however, may easily be divided into simple fractions, and the measuring of drops, teaspoons, tablespoons, etc., is readily understood by the laity.

Apothecaries' Weights and Measures

In writing prescriptions in the apothecaries' system the various denominations for weight and volume are designated by certain symbols or abbreviations, followed by the amount indicated in Roman numerals. For example: gr. = grains; ʒ = drachms; ℥ = ounces; ♏ = minim; fʒ = fluidrachm; f℥ = fluidounce; O = pint.

In writing prescriptions in the apothecaries' system Roman, *not* Arabic, numerals are employed. The quantity is repeated by the figures with a dot over the ones, the last one usually being written as a j, thus: i, ij, iij, iv, vj, x, xxj, xl, l, etc. Fractions are written as common fractions and not as decimals: gr. 1/10, not gr. 0.1.

APOTHECARIES' (OR TROY) WEIGHTS
(For Weighing Solid Medicines)

20 grains (gr.)	=	1 scruple (℈)
3 scruples (℈)	=	1 drachm (ʒ)
8 drachms (ʒ)	=	1 ounce (℥)
12 ounces (℥)	=	1 pound (lb.)

The scruple, either symbol or weight, is very rarely, if ever, used in prescription writing.

APOTHECARIES' OR WINE MEASURES
(For Measuring Liquid Medicines)

60 minims (♏)	=	1 fluidrachm (fʒ)
8 fluidrachms (fʒ)	=	1 fluidounce (f℥)
16 fluidounces (f℥)	=	1 pint (O)

Metric System

The metric system is a decimal system, the denominations increasing by tens and decreasing by tens. From the unit of length (meter) are obtained the units of weight (gram) and the units of capacity (liter).

The unit of the metric system is the meter—39.37 inches. The unit of measure of volume is the liter. A container that is one-tenth of a meter in each of its dimensions will hold a liter. The unit of weight is the gram, the weight of one cubic centimeter of water at 4° Centigrade.

Greater or lesser quantities are designated by either Latin or Greek prefixes for 10, 100, 1,000, and 10,000. The Latin prefixes are *deci* (one-tenth), *centi* (one-hundredth), and *milli* (one-thousandth). The Greek prefixes are *deka* (ten), *hecto* (hundred), *kilo* (thousand), and *myria* (ten thousand).

In prescription writing we use only two units, grams and cubic centimeters, abbreviated Gm. and cc. In metric prescribing the

numerals precede the abbreviations and are written in the Arabic characters, thus: 5 Gm.; 2 cc. To distinguish the abbreviation for gram (Gm.) from that for grain (gr.) the former is written with a capital, and the latter with a small letter. Fractions of grams or cubic centimeters are expressed by decimals, as: 1.2 cc., 0.003 cc., 0.5 Gm., 5.50 Gm.

Metric Measures

(For Weighing Solid Medicines)

1 milligram (1 mg.)	=	0.001 gram (Gm.)
1 centigram	=	0.01 gram
1 decigram	=	0.1 gram
1 gram	=	the weight of 1 cc. of water at 4° C.
1 kilogram	=	1000 grams

Metric Fluid Measures

(For Measuring Liquid Medicines)

1 cubic centimeter (1 cc.)	=	0.001 liter
1,000 cubic centimeters (1,000 cc.)	=	1.0 liter

The above-mentioned weights and measures are used in writing prescriptions, but when drugs are bought and sold in large quantities the avoirdupois weights are employed.

Avoirdupois Weights

437.5 grains (gr.)	=	1 ounce (oz.)
16 ounces	=	1 pound (lb.)
100 pounds	=	1 hundredweight (cwt.)

An avoirdupois pound contains 7,000 grains or 16 ounces of 437.5 grains each, while a troy (apothecaries') pound contains 5,760 grains, or 12 ounces of 480 grains each.

Tables I, II, and III are given to show the relationship between the two systems of weights and measures. For rapid approximate transpositions of the metric into the apothecaries' or the reverse, the approximate figures are considered sufficiently accurate. The student should learn the accompanying tables.

Table I

Equivalent Weights and Measures

Apothecaries' Systems	℞ Symbol	Metric Appr.	Equivalents Exact
1 Minim*	♏	0.06 cc.	0.06161 cc.
1 Grain	gr.	60 mg.	64.8 mg.
1 Scruple	℈	1.3 Gm.	1.296 Gm.
1 Fluidrachm	f3 or 3	4 cc.	3.697 cc.
1 Drachm	3	4 Gm.	3.888 Gm.
1 Fluidounce	f℥ or ℥	30 cc.	29.57 cc.
1 Ounce	℥	31 Gm.	31.103 Gm.
1 Pint	O	475 cc.	473.167 cc.

*The volume measure "minim" should not be used interchangeably for the approximate measure "drop." The size of a drop is a function of the viscosity, specific gravity, and temperature of the liquid; thus 48 drops of water measure 1 fldr., whereas 234 drops of chloroform are required to produce the same volume. Fluid potent remedies should always be measured and not dropped from the container.

METRIC SYSTEM	APOTHECARIES' APPR.	EQUIVALENTS EXACT
1 Milligram (mg.)	1/60 gr.	0.0154 gr.
1 Gram (Gm.)	15 gr.	15.432 gr.
1 Cubic Centimeter (cc.)	15 ♏	16.23 ♏
1 Liter (L)	33.8 f℥	33.81 f℥

TABLE II

EQUIVALENTS

FRACTIONS OF GRAIN	METRIC EQUIVALENTS, GRAMS
1/2	0.03
1/3	0.02
1/4	0.015
1/6	0.010
1/8	0.008
1/10	0.006
1/12	0.005
1/15	0.004
1/30	0.002
1/60	0.001
1/100	0.0006
1/120	0.0005
1/150	0.0004
1/200	0.0003
1/300	0.0002
1/600	0.0001

HOUSEHOLD MEASURES

1 drop (gtt.)	1 minim	0.06 cc.
1 teaspoonful	1 f3	4.00 cc.
1 dessertspoonful	2 f3	8.00 cc.
1 tablespoonful	4 f3	16.00 cc.
1 teacupful	4 f℥	125.00 cc.
1 glassful	8 f℥	250.00 cc.

TABLE III

MISCELLANEOUS CONVERSION TABLES

Inch	2.54 cm.
Meter	39.37 inches
Ounce Avoir.	28.35 grams
Ounce Troy	31.10 grams
Pound Avoir.	453.59 grams
Pound Troy	373.24 grams
Gallon U. S.	3.7854 liters
Gallon U. S.	231.00 cu. inches

Converting Grains, Drachms, and Ounces to Grams or cc.

1. Divide the number of grains by 15.
2. Multiply the number of drachms by 4.
3. Multiply the number of ounces by 30.

The result in each equals approximately the number of grams or cc.

SIZES OF PRESCRIPTIONS

Quantities of pharmaceutical preparations used in prescriptions should be limited to minimum requirements of cases. The custom of prescribing in quantities too large places an unnecessary expense on the patient and the unused portion remains as a monument to the doctor's poor judgment. There is always the possibility of the medicines being used indiscriminately for other illnesses, with disastrous results. The following list represents the amount usually prescribed at one time.

Standard containers are supplied as follows: bottles for fluids, 15, 30, 60, 120, 180, 240, 360, and 480 cc. (½, 1, 2, 4, 5, 8, 12, and 16 ounces); boxes for capsules, pills and tablets, to hold 12, 50, 100 each of these dosage forms; ointment jars to hold 15, 30, 60, 90, 120, and 240 grams (½ to 8 ounces).

The size of a prescription will vary, depending on the purpose for which it is intended. The following are common sizes used.

Cough mixtures	120 to 200 cc. (f℥ 4 to 8)
Capsules, Pills, Powders	6 to 24
Emulsions	120 to 200 cc. (f℥ 4 to 8)
Lotions	120 to 200 cc. (f℥ 4 to 8)
Eye lotions ("drops")	15 to 30 cc. (f℥ ½ to 1)
Injections, hypodermic or intramuscular	up to 2 cc. (up to ♏ 30)
Injections, intravenous	up to 200 cc. (up to f℥ 8)
Liniments	200 to 400 cc. (f℥ 6 to 12)
Mouthwashes, Gargles	60 to 150 cc. (f℥ 2 to 6)
Ointments	15 to 240 Gm. (℥ ½ to 8)

SPECIFYING MANUFACTURERS

There is a tendency on the part of the members of the medical profession to specify on the prescriptions the preparation of some particular manufacturer. Promiscuous specifying of special makes is usually a sign of ignorance, as the present State and National laws have practically forced a uniformly high standard in manufacturing.

DOSAGE

The dose of a drug to be given a patient is largely a matter of judgment. The Pharmacopoeia assigns to each drug and preparation what may be considered an "average adult dose" an amount which usually produces a therapeutic effect for which the substance is commonly employed, that is, once a day, twice a day, or at more frequent intervals. This average dose may be increased or decreased by the physician to meet adequately the existing circumstances. As a rule the U.S.P., N.F., and N.N.R. do not list the total dosage or the number of times the doses are to be given; this naturally rests with the physician.

The *minimum dose* is the smallest dose capable of producing a therapeutic effect. A *maximum dose* is the largest dose that can be administered without producing poisonous effects. A *toxic dose* is a poison dose. Physicians must remember that different persons will respond differently to the same dose of the same drug. The term "minimal lethal dose" (M.L.D.) is the smallest dose producing death. It is important for bioassays and the evaluation of margins of safety in drug studies.

Certain factors should be taken into consideration in determining the drug dosage. The conditions that modify the action of drugs have been previously discussed. These factors should be considered before

the dosage of any drug is decided upon. Of this group the factors most liable to effect the actual needs of the patient are age, weight, sex, idiosyncrasy, tolerance, and disease. These factors not only modify the single dose of a drug, but also the amount which can be given in a day.

The **frequency of the dosage** is determined by the condition of the patient or, if continued effect is desired, by the rate of elimination of the drug. Disease affecting the excretory organs naturally plays an important role in determining the frequency of administration of drugs. Epinephrine, caffeine, chloral hydrate, iodides, salicylates, physostigmine salicylate, solution of pituitary, and strychnine are eliminated within a few hours, hence the intervals of repetition of administration are measured in hours. Arsenic, barbituric acid derivatives, bromides, digitalis, mercurial preparations, and thyroid are eliminated more slowly, hence repetition of administration is measured in days. The following examples illustrate the rapidity of drug action:

Drugs which act rapidly are:

Alcohol	Caffeine	Salicylates
Ammonia	Chloral	Strychnine
Camphor	Iodides	

(Act in 1 minute to 1 hour)

Drugs which act slowly are:

Arsenic	Digitalis	Synthetic antipyretics
Atropine	Mercury	Synthetic hypnotics
Bromides	Quinine	Thyroid

(Act in several hours to 20 hours)

Drugs which tend to accumulate are:

Arsenic	Bromides	Mercury
Atropine	Digitalis	Strychnine

Some drugs, such as narcotics, bromides, most metals, gland extracts, most cathartics, and quinine, are excreted in the milk. Therefore keep in mind that the baby may suffer from the treatment given the nursing mother.

The Pharmacopoeia and the National Formulary assign to each drug and to most preparations an *official dose*. These doses are for adults and are small enough to be safe under nearly all circumstances. In actual practice larger doses are usually necessary. The dose for a child is usually estimated as being a fractional part of the adult dose.

Dosage for Children.—Doses for children follow no definite rule. Certain drugs, such as arsphenamine, atropine, digitalis, and the sulfonamides, are given to children in relatively larger doses than to adults. Opiates, on the other hand, are relatively less well tolerated by infants and children than by adults. Certain rules are, however, of assistance in determining doses suitable for children. The following rules are useful:

Clark's Rule.—Divide the weight of child in pounds by the average weight of adult (150), and take this fraction of the adult dose. Example:

Weight of child 50 pounds
Adult dose 0.6 gram

$$\text{Therefore } \frac{50}{150} \times 0.6 \text{ gram} = 0.2 \text{ gram child's dose.}$$

This rule gives the best results and is based on scientific principles.

Young's Rule is the most commonly used. This rule is based upon the age of the child, regardless of weight. Divide age of child by age plus 12, and the resulting fraction is the portion of the adult dose to use. Thus for a child 6 years old the fraction would be

$$\frac{6}{6 + 12} \text{ or } \frac{1}{3} \text{ of the adult dose.}$$

Cowling's Rule uses a fraction obtained by taking the child's age at its next birthday for the numerator and 24 as the denominator. Thus for a child of 2 years the fraction would be $\frac{3}{24}$ or $\frac{1}{8}$ of the adult dose.

In comparison with the weight curve, the results obtained by this rule are low for children under 4 years of age or over 15 years.

Dilling's Rule divides the actual age of the child by 20 to form the fraction in calculating the doses.

At 20 years, the adult dose.
At 10 years, $\frac{1}{2}$ the age, $\frac{1}{2}$ the dose.
At 5 years, $\frac{1}{4}$ the age, $\frac{1}{4}$ the dose.
At 2½ years, $\frac{1}{8}$ the age, $\frac{1}{8}$ the dose.
At 1 year, $\frac{1}{12}$ the dose (exception).

Fried's Rule for Infants.—In case the age is less than one year the following method may be used in figuring the dosage. Divide age in months by 150 and multiply it by the adult dose. For a baby of 6 months the dose would be $\frac{6}{150}$ or $\frac{1}{25}$ times the adult dose.

Dosage for Aged People.—In old age, the dose must be, as a rule, somewhat less than that for adults. Irritant cathartics, emetics, narcotics, and depressant drugs should be administered with caution to old people. Above sixty years, the adult dose is reduced to four-fifths or two-thirds, and even to one-half in extreme senility.

Memorizing of Dosages

The student *must learn* the doses of the most commonly used drugs. This is not the task that it might appear to be if the dosage is learned with the drug almost as part of the name of the drug. For example, think of morphine sulfate and the dosage 10 mg. (⅙ grain) as one and as being inseparable. Rules of various kinds are of little value as aids for remembering dosages. However, a few general principles are worth remembering. Remember that:

	STRENGTH	DOSE
Powders (crude drug)	100%	0.3-2 Gm.
Fluidextracts (100 Gm. crude to 100 cc.)	100%	0.06-2 cc.
Extracts (200 to 800 Gm. crude to 100 Gm. extract)	200 to 800%	0.015-0.3 Gm.
Tinctures (10 Gm. crude to 100 cc.)	10%	0.5-2 cc.
Tinctures (less potent)	20%	4 cc.
Infusions	1 to 80%	usually 2-30 cc.
Decoctions (5 Gm. to 100 cc.)	5%	variable
Spirits		usually 15-30 minims
Elixirs		usually 4 cc.
Syrups		0.95 to 10 cc.
Aromatic Waters		15 cc.

VEHICLES

A vehicle is a medium in which medicine is administered. It is generally employed in sufficient quantity to make a dose a readily measurable amount. Examples: Syrups and aromatic waters in liquid preparations; lard and wool fat in ointments; liquid petrolatum in sprays, etc. They are relatively inert solutions, semisolids or solids, generally employed in sufficient quantity to make the dose measurable. The selection of the proper vehicle in the writing of prescriptions is of great importance; the apparent reason proprietary remedies are so popular is that they are dispensed in attractive and pleasant vehicles.

Vehicles may be classified as follows: (A) flavoring vehicles, (B) coloring agents, (C) solid and semisolid vehicles, and (D) excipients.

Flavoring and Coloring Vehicles

A large number of preparations are used in prescriptions for flavoring and coloring, some preparations serving a dual purpose. Usually flavoring or coloring is applied only to liquid preparations for oral administration. However, *powders* may be flavored or even colored, and *pills* or *tablets* may be coated with sugar to conceal undesirable tastes and even colored to appear more attractive. In selecting a vehicle for a liquid prescription the physician must take into account the following:

Solubility.—It is usually desirable to administer a drug in solution, hence the vehicle chosen must naturally be one that will dissolve the drug. In general, alcoholic vehicles, such as elixirs, tinctures, fluidextracts, and spirits, have a relatively greater solvent action for alkaloids, oils, resins, etc., than aqueous preparations. Aqueous preparations usually are much more solvent for salts and gums.

Reaction.—The reaction of the vehicle plays an important part in its selection, especially because the acidity or alkalinity often affects the color produced; furthermore a precipitation, with formation of different compounds, results if ingredients of opposite reaction are placed in the same liquid prescription. Examples: Carmine Solution, N.F., is of a purplish-red color in an alkaline medium, a bright red in a neutral medium, and precipitates when the reaction is acid. Glycyrrhiza Fluidextract, U.S.P., precipitates when the reaction becomes acid, because ammonium hydroxide is added to the preparation to dissolve the glucoside, glycyrrhizin.

Taste.—The taste of a preparation is an important element in securing the best of therapeutic results. A disagreeable preparation may cause nausea and vomiting and in the end be refused by the patient entirely. The ability to prescribe a pleasant and agreeable medicine is important in securing the cooperation of the patient.

Color.—Coloring is almost equally as desirable as a suitable flavoring. Often the flavoring provides the color, e.g., Compound Cardamom Tincture, U.S.P., B.P., Wild Cherry Syrup, U.S.P., etc.

Incompatibility.—In selecting a vehicle one must be selected that is capable of existing harmoniously with the other ingredients of the prescription. The task of securing compatible prescriptions is not as difficult as it might seem if the general rules on incompatibility listed in this chapter are adhered to.

Select a Simple and Inexpensive Vehicle.—Inexpensive vehicles should be chosen, provided they are satisfactory for the prescription. Water is one vehicle which should be employed whenever possible. The aromatic waters, such as Peppermint Water, U.S.P., B.P., Fennel Water,

U.S.P., etc., are excellent vehicles for disguising the taste of many salts. Aromatic Elixir, U.S.P., is a good solvent, possesses an agreeable taste, and is indicated in the prescribing of many salts and alkaloidal salts. Wild Cherry Syrup, U.S.P., B.P., and Syrup of Tolu, U.S.P., B.P., are excellent cough remedies. Cacao Syrup, N.F., and Aromatic Eriodictyon Syrup, N.F., are excellent vehicles for quinine prescriptions. Liquid Petrolatum, U.S.P., is often used in prescribing oil-soluble drugs; Medicinal Soft Soap, U.S.P., B.P., is useful in prescribing liniments; Lactose, U.S.P., B.P., is commonly used in prescribing powders. Petrolatum, U.S.P., Lard, U.S.P., B.P., and Wool Fat, U.S.P., B.P., are excellent vehicles for various ointments.

A. Flavoring Vehicles

Flavoring is an important factor in preparing medicine to be taken by mouth. It consists of imparting a suitable taste to a preparation and it also consists in disguising disagreeable tastes. Improving the tastes of medicines may be accomplished by dilution, by sweetening, by the use of mucilages, acids, syrups, spirits, elixirs, and tinctures, and by the use of drugs which paralyze the taste buds. It is well to bear in mind that large doses may be taken with cereal or in thick soup. Milk or tea may be used effectively for administering drugs. Plain water, preferably cold, may aid in masking the taste of an ill-tasting medicine, if given immediately following the ingestion.

The use of flavoring is especially important in dispensing prescriptions to women and children. Since tastes vary widely in individuals, it is well to consult the patient to determine his likes and dislikes before prescribing medicine for his use. Flavoring vehicles may be divided into two groups.

1. **Aqueous Vehicles.**—The aqueous vehicles most commonly used for flavoring purposes are the aromatic waters, syrups, and to a lesser extent the mucilages.

a. **Aromatic Waters,** or Aquae, are suitable vehicles for water-soluble salts and other disagreeable-tasting substances. In aromatic waters the quantity of active substance is sufficient to give a pleasant flavor without imparting any noticeable therapeutic properties. Waters do not keep well. The following are common aromatic waters. For external use Rose Water is often used.

Preparations

Anise Water, *Aqua Anisi,* U.S.P. A saturated solution of oil of anise in distilled water. *Dosage:* 15 cc. (4 fluidrachms).

Camphor Water, *Aqua Camphorae,* U.S.P., B.P. Saturated solution of camphor in distilled water. *Dosage:* 10 cc. (2½ fluidrachms).

Chloroform Water, *Aqua Chloroformi,* N.F., B.P. Saturated solution of chloroform in distilled water. *Dosage:* 15 cc. (4 fluidrachms).

Cinnamon Water, *Aqua Cinnamomi,* U.S.P. Saturated solution of cinnamon oil in distilled water. *Dosage:* 15 cc. (4 fluidrachms).

Fennel Water, *Aqua Foeniculi,* U.S.P. A saturated solution of fennel oil in water. *Dosage:* 15 cc. (4 fluidrachms).

Peppermint Water, *Aqua Menthae Piperitae,* U.S.P. A saturated solution of peppermint oil in distilled water. *Dosage:* 15 cc. (4 fluidrachms).

Spearmint Water, *Aqua Menthae Viridis,* U.S.P. A saturated solution of spearmint oil in water. *Dosage:* 15 cc. (4 fluidrachms).

Rose Water, *Aqua Rosae,* U.S.P. A mixture of stronger rose water with distilled water.

Stronger Rose Water, *Aqua Rosae Fortior*, U.S.P. Prepared by distilling fresh cabbage roses with water.

b. **Syrups** are useful when a water solvent accompanied by a sweet taste is wanted. Keep in mind high sugar content (diabetic patients). When mixed with strong alcohol the sugar may crystallize out. Usually syrups are used as vehicles, but in some cases they constitute the full medication, e.g., Ferrous Iodide Syrup, Ipecac Syrup.

PREPARATIONS

Syrup, *Syrupus*, U.S.P., B.P. Sucrose (85%) in distilled water.

Acacia Syrup, *Syrupus Acaciae*, N.F. Acacia (10%) with sodium benzoate, vanilla tincture, sucrose, and distilled water.

Citric Acid Syrup, *Syrupus Acidi Citrici*, U.S.P. Citric acid (1%), flavored with lemon tincture, in syrup. For ammonium chloride, and citrates; incompatible with alkaline carbonates. CAUTION—this preparation must not be dispensed if it has a terebinthinate odor or taste, or shows other indications of deterioration.

Orange Syrup, *Syrupus Aurantii*, U.S.P., B.P. Sweet orange peel tincture, citric acid, and sucrose in distilled water. For ammonium chloride, citrates, bitter drugs; incompatible with alkaline carbonates. CAUTION—this preparation must not be dispensed if it has a terebinthinate odor or taste, or shows other indications of deterioration.

Cacao Syrup, *Syrupus Cacao*, N.F. Prepared Cacao (17.5%) vanilla tincture, gelatin, sucrose, and distilled water. Absolute alcohol content about 2 per cent. For atropine, caffeine, chloral hydrate, ephedrine, quinine, and all bitter drugs.

Aromatic Eriodictyon Syrup, *Syrupus Eriodictyi Aromaticus*, N.F. Eriodictyon fluidextract, potassium hydroxide solution, compound cardamom tincture, sassafras oil, lemon oil, clove oil, alcohol, sucrose, magnesium carbonate and distilled water. Absolute alcohol content about 7 per cent. *Dosage:* 8 cc. (2 fluidrachms).

Glycyrrhiza Syrup, *Syrupus Glycyrrhizae*, U.S.P. Glycyrrhiza fluidextract (25%) in fennel oil, anise oil, and syrup. *Dosage:* 8 cc.

Wild Cherry Syrup, *Syrupus Pruni Virginianae*, U.S.P. Wild cherry (15%), in glycerin, sucrose, alcohol, and distilled water. Absolute alcohol content about 1.5 per cent. *Dosage:* 10 cc.

Raspberry Syrup, *Syrupus Rubi Idaei*, N.F. Juice of ripe raspberries in sucrose, alcohol, and distilled water. Absolute alcohol 1 to 2 per cent.

Compound Sarsaparilla Syrup, *Syrupus Sarsaparillae Compositus*, U.S.P. Sarsaparilla fluidextract (20%), glycyrrhiza fluidextract, sassafras oil, anise oil, methyl salicylate, and alcohol in syrup. Absolute alcohol content about 10 per cent. For ammonium chloride, potassium iodide, sodium bromide, and sodium salicylate. *Dosage:* 15 cc.

Sweetening Agents.—The usual sweetening agents are sucrose, glucose, saccharin, and honey. Other sugars, such as fructose, lactose, and maltose, may be used. Sucrose is usually used in the form of its saturated watery solution or syrup. This saturated solution may be improved by flavors, such as glycyrrhiza or tolu, or by the addition of aromatics, such as in Aromatic Elixir.

Saccharin is used for diabetic patients and in pill coating. Renewed interest in the possible harmful effect of this substance is apparent. Earlier investigations of saccharin, however, have failed to reveal

dangerous side reactions except from extremely large doses. Likewise, the evidence does not reveal any reason why saccharin cannot be used continuously in average sweetening doses for an indefinite period. Many patients have taken saccharin for years without harmful effect. Lactose is often used in sweetening powders and in the manufacture of pills.

Relative Sweetening Power of Agents.—If sucrose is taken as 100, then levulose is about 175, glucose 75, maltose and galactose 33, lactose 16. Saccharin is 300 to 500 times as sweet as sucrose.

PREPARATION

Saccharin Sodium, *Saccharinum Sodicum*, U.S.P., B.P. Colorless or white powder, odorless or nearly so with an intensely sweet taste. Freely soluble in water (1 in 1.5) and soluble in alcohol (1 in 50). Sweetening agent, especially for diabetic patients. 0.03 Gm. is the equivalent of 1 ordinary lump of sugar. For general sweetening use in proportion 1:10,000.

c. MUCILAGES are suitable vehicles for water-soluble substances. They are often employed in the preparation of emulsions and suspensions. Mucilages are incompatible with alcohol and should be freshly prepared, as they do not keep well.

PREPARATIONS

Acacia Mucilage, *Mucilago Acaciae*, U.S.P. Acacia (35%) with benzoic acid (0.2%) in water. B.P., Acacia (35%) in aqueous solution of benzoic acid. CAUTION—Acacia Mucilage must not be dispensed if it has become sour or moldy.

Tragacanth Mucilage, *Mucilago Tragacanthae*, U.S.P. Tragacanth (6%) in glycerin (18%) and aqueous solution of benzoic acid. Used for suspending insoluble powders for external use; used in lotions (1-2%). B.P., Tragacanth (1.25%) in chloroform water.

2. **Alcoholic Vehicles.**—Alcoholic vehicles are suitable as either vehicles or flavoring agents for substances soluble in alcohol. They are suitable for flavoring syrups. The properties of alcohol, such as ability to dissolve insoluble oils, alkaloids and resins, preservative action, ability to precipitate certain aqueous solutions, its pharmacological action, must be remembered.

a. ELIXIRS are sweetened aromatic alcoholic solutions, used similarly to syrups as flavoring vehicles. Their alcoholic content is usually 25 per cent. High sugar content should be borne in mind when prescribing for diabetic patients.

PREPARATIONS

Compound Benzaldehyde Elixir, *Elixir Benzaldehydi Compositum*, N.F. Benzaldehyde (0.05%), vanillin, orange flower water, alcohol (5%), syrup, and distilled water.

Aromatic Elixir, *Elixir Aromaticum*, U.S.P. Compound orange spirit in syrup, purified talc, alcohol and distilled water. Absolute alcohol content about 23 per cent. It has a pleasant orange flavor, and is useful for dissolving drugs that are more soluble in alcohol than in water. It is particularly suitable for disguising the nauseating taste of sodium salicylate.

Red Aromatic Elixir, *Elixir Aromaticum Rubrum*, N.F. Aromatic elixir colored with cudbear. Absolute alcohol content about 23 per cent.

Glycyrrhiza Elixir, *Elixir Glycyrrhizae*, N.F. Glycyrrhiza fluidextract (12:5%) and aromatic elixir. Absolute alcohol content about 22 per cent.

Iso-Alcoholic Elixir, *Elixir Iso-Alcoholicum*, N.F. A mixture of low-alcoholic elixir (8 to 10 per cent of C_2H_5OH) and a high-alcoholic elixir (73 to 78 per cent C_2H_5OH) in definite proportions and intended to serve as a general vehicle for various medicaments that require solvents of certain alcoholic strengths.

b. SPIRITS, or alcoholic solutions of volatile drugs, contain about 50 per cent alcohol; used in small quantities as flavors added to other vehicles for flavoring purposes.

PREPARATIONS

Anise Spirit, *Spiritus Anisi*, N.F. Anise oil (10%) in alcohol. Absolute alcohol content about 84 per cent. *Dosage:* 1 cc. (15 minims).

Peppermint Spirit, *Spiritus Menthae Piperitae, U.S.P.*, B.P. Peppermint oil (10%), colored with peppermint in alcohol. Absolute alcohol content about 82 per cent. *Dosage:* 1 cc. (15 minims).

Spearmint Spirit, *Spiritus Menthae Viridis*, U.S.P. Spearmint oil (10%), colored with spearmint in alcohol. Absolute alcohol content about 82 per cent. *Dosage:* 1 cc. (15 minims).

Compound Vanillin Spirit, *Spiritus Vanillini Compositus*, N.F. Vanillin, orange oil, cardamom oil, cinnamon oil, and alcohol. Absolute alcohol content about 68 per cent.

c. TINCTURES may also be used as vehicles. The alcohol content varies from 45 to 76 per cent; they usually cloud upon addition of water.

PREPARATIONS

Bitter Orange Peel Tincture, *Tinctura Aurantii Amari*, U.S.P. Bitter orange peel (20%) in alcohol and distilled water. Absolute alcohol content about 60 per cent. *Dosage:* 4 cc. (1 fluidrachm).

Sweet Orange Peel Tincture, *Tinctura Aurantii Dulcis*, U.S.P.; Tinctura Aurantii, B.P. Sweet orange peel from fresh fruit (50%) in alcohol. Absolute alcohol content about 75 per cent. *Dosage:* 4 cc. (1 fluidrachm).

Tolu Balsam Tincture, *Tinctura Balsami Tolutani*, U.S.P. Tolu balsam tincture (5%) with magnesium carbonate and distilled water. *Dosage:* 10 cc. (2½ fluidrachms).

Compound Cardamom Tincture, *Tinctura Cardamomi Composita*, U.S.P., B.P. Cardamom seed (2%), cinnamon, caraway, and cochineal in diluted alcohol and glycerin. Absolute alcohol content about 45 per cent. *Dosage:* 4 cc. (1 fluidrachm).

Compound Gentian Tincture, *Tinctura Gentianae Composita*, U.S.P., B.P. Gentian (10%), bitter orange peel and cardamom seed in glycerin, alcohol, and distilled water. Absolute alcohol content about 45 per cent. *Dosage:* 4 cc. (1 fluidrachm).

Compound Lavender Tincture, *Tinctura Lavandulae Composita*, U.S.P. Lavender oil, rosemary oil, cinnamon, clove, myristica, and red saunders in alcohol and water. Absolute alcohol content about 70 per cent. *Dosage:* 2 cc. (30 minims).

Lemon Tincture, *Tinctura Limonis*, U.S.P., B.P. Fresh lemon peel (50%) treated with alcohol. Absolute alcohol content about 73 per cent.

Practical Flavoring.—A pleasant flavor may add much to the effectiveness of a prescription. In the matter of taste we distinguish four primitive taste sensations, sweet, sour, bitter, and salt; some

authors add to these alkaline and metallic tastes. The following means are suggested for the improving and disguising of the tastes of liquid medicines.

1. *Sweet Taste.*—Aromatic Elixir, U.S.P., Glycyrrhiza Elixir, N.F., and simple dilution.
2. *Sour Taste.*—Compound Sarsaparilla Syrup, U.S.P., Cacao Syrup, N.F., Raspberry Syrup, N.F.
3. *Bitter Taste.*—Aromatic Eriodictyon Syrup, N.F., Cacao Syrup, N.F., Raspberry Syrup, N.F.; for children, Glycyrrhiza Syrup, U.S.P., Fennel Water, U.S.P., Anise Water, U.S.P., Tolu Balsam Tincture (Syrup of Tolu), U.S.P. (the latter is excellent for cough remedies).
4. *Salt Taste.*—Orange Syrup, U.S.P., B.P., Peppermint Water, U.S.P., B.P. Compound Sarsaparilla Syrup, U.S.P., Glycyrrhiza Elixir, N.F., Saccharin Sodium, U.S.P., B.P., carbonated water, milk, or simple dilution.
5. *Alkaline Taste.*—Cacao Syrup, N.F., Peppermint Water, U.S.P., B.P., milk, or carbonated water.
6. *Metallic Taste.*—Orange Syrup, U.S.P., B.P., Aromatic Eriodictyon Syrup, N.F.

Relative Worth of Flavors.—The relative worth of various vehicles of the U.S.P. and N.F. as agents to disguise the tastes of ammonium chloride and quinine hydrochloride has been satisfactorily established by Purdum (1942).

AMMONIUM CHLORIDE	QUININE HYDROCHLORIDE
1. Glycyrrhiza Syrup	1. Syrup of Prepared Cacao, N.F. (?) VI
2. Raspberry Syrup, N.F.	2. Glycyrrhiza Syrup
3. Orange Flower Syrup	3. Cacao Syrup, N.F.
4. Citric Acid Syrup	4. Aromatic Eriodictyon Syrup, N.F.
5. Syrup of Tolu	5. Thyme Syrup, N.F.
6. Acacia Syrup, N.F.	6. Glycyrrhiza Elixir, N.F.
7. Orange Syrup	7. Syrup of Tolu
8. Aromatic Eriodictyon Syrup, N.F.	8. Compound Sarsaparilla Syrup
9. Cherry Syrup, N.F.	9. Raspberry Syrup, N.F.
10. Cacao Syrup, N.F.	10. Cherry Syrup, N.F.

B. Coloring Agents

The selection of the proper coloring agent is almost as important as flavoring. In some cases the vehicle chosen provides both the coloring and flavoring. The usual colors for internal use are red, brown, and yellow. Table IV lists colors which are employed in proportions of about 1 per cent.

Alkanet in the form of 10 per cent tincture (unofficial) is satisfactory for coloring oils red.

Carmine (powder) is used to color ointments and dental preparations.

Preparations

Caramel, *Caramel*, N.F. Dark Brown, syrupy, somewhat bitter liquid. Freely soluble in water and in diluted alcohol; insoluble in 80 per cent alcohol.

Glycyrrhiza Fluidextract, *Fluidextractum Glycyrrhizae*, U.S.P. Glycyrrhiza (100%). Absolute alcohol content about 22 per cent. *Dosage:* 2 cc. (30 minims).

TABLE IV

TABLE OF COLORING AGENTS

Red Colors

COLORING AGENTS	SOLUBLE IN		COLOR REACTION			SUITABLE FOR COLORING
	WATER	ALCOHOL	ACID	NEUTRAL	ALKALINE	
Cudbear Tincture N.F.	Yes	Yes	Red (sl. ppt.)	Deep red	Purple red	For aqueous and alcoholic solutions; acid, alkaline, and neutral
Cochineal Solution N.F.	Yes	Sl.	Red (sl. ppt.)	Bright red	Purplish red	For aqueous and alcoholic solutions; acid, alkaline, and neutral
Amaranth Solution U.S.P.	Yes	Sl.	Magenta red	Magenta red	Dark red	Aqueous liquids, alcoholic liquids (up to 50%) neutral, alkaline, or acid.
Compound Cardamom Tincture U.S.P.	Yes	Yes	Bright violet-crimson	Violet-crimson	Deep violet-crimson	For aqueous and alcoholic solutions; acid, alkaline, and neutral
Compound Lavender Tincture U.S.P.	Sl.	Yes	Red	Reddish purple	Purple	For alcoholic or hydro-alcoholic solutions (aqueous solutions may require filtration); acid, alkaline, and neutral
Carmine Solution N.F.	Yes	Sl.	Ppt.	Bright red	Purplish red	Neutral or alkaline aqueous or alcoholic (up to 50%) liquids

Brown Colors

Compound Cudbear Tincture N.F.	Yes	Yes	Brown	Reddish brown	Dark red to purplish	For aqueous and alcoholic solutions; acids, alkaline, and neutral
Caramel N.F.	Yes	Yes	Brown	Brown	Brown (dark)	For aqueous and alcoholic solutions; acid, alkaline, and neutral

TABLE IV—CONT'D

COLORING AGENTS	SOLUBLE IN		COLOR REACTION			SUITABLE FOR COLORING
	WATER	ALCOHOL	ACID	NEUTRAL	ALKALINE	
Glycyrrhiza Fluidextract U.S.P.	Yes	Yes	Ppt.	Brown	Brown	For aqueous and alcoholic solutions; alkaline and neutral solutions (not acid)
Yellow Colors						
Hydrastis Tincture N.F.	Sl.	Yes	Yellow	Yellow	Yellow	Neutral, alkaline, or acid alcoholic or hydroalcoholic liquids (aqueous liquids may be cleared by filtration)
Curcuma Tincture N.O.	Yes (sl. ppt.)	Yes	Yellow	Yellow	Reddish brown	Neutral, acid alcoholic liquids (aqueous solutions ppt. but may be filtered)

Amaranth Solution, *Liquor Amaranthi*, U.S.P. Amaranth (1%) in distilled water.

Carmine Solution, *Liquor Carmini*, N.F. Carmine in ammonia water, glycerin, and water.

Cochineal Solution, *Liquor Cocci*, N.F. Cochineal (6.5%), potassium carbonate, alum, potassium bitartrate, glycerin, and distilled water.

Curcuma Tincture, *Tinctura Curcumae*, Nonofficial.

Hydrastis Tincture, *Tinctura Hydrastis*, N.F. Hydrastis (20%) yielding about 0.5 per cent of alkaloids; in alcohol and water. Absolute alcohol content about 60 per cent. *Dosage:* 8 cc. (2 fluidrachms).

Cudbear Tincture, *Tinctura Persionis*, N.F. Cudbear in alcohol and water. Absolute alcohol content about 64 per cent.

Compound Cudbear Tincture, *Tinctura Persionis Composita*, N. F. Tincture of cudbear and caramel in alcohol and water. Absolute alcohol content about 22 per cent.

C. Solid and Semisolid Vehicles

1. Creams.—These preparations may be defined as mixtures of fat or fatlike substances bound together with water through physical-chemical intermediaries. *Hydrous wool fat* has for years been used for the manufacture of creams. *Saponified creams* are also useful but are unable to tolerate electrolytes.

The sulfonated oils are valuable binding agents of the physical-chemical class. *Diglycol laurate* and *diglycol stearate* are useful new chemicals for binding or emulsifying nonmiscible fats and water. The

higher alcohols, including stearyl, octyl, and cetyl alcohol, are important constituents of creams. As little as 2 per cent *cetyl alcohol* improves any cream. It also causes the skin to assume a velvety sheen and feel. It assists in combining fat and fatlike substances with water.

Glyceryl monostearate is an excellent emulsifier and binding agent. Preparations containing this substance are little affected by change in pH and are not incompatible with acid or alkaline remedies.

Sulfonated oils, such as sulfonated castor oil or sulfonated olive oil, are available in all degrees of sulfonation. They are useful constituents of soapless shampoo ingredients and rarely cause any skin reactions. The light or heavy U.S.P. liquid petrolatum should not be used in dermatological preparations, but a low viscosity (55-80) petrolatum is recommended.

The following creams are useful:

VANISHING CREAM

℞

Glyceryl Monostearate	12 Gm.
Yellow Wax	2 Gm.
Glycerin	6 cc.
Corn Oil	4 cc.
Water qs.ad	100 Gm.

HAND CREAM

℞

Glyceryl Monostearate	16 Gm.
Lanolin, Hydrous	4 Gm.
Cetyl Alcohol	1 Gm.
Liquid Petrolatum	4 cc.
Cotton Seed Oil	4 cc.
Corn Oil	4 cc.
Water qs.ad	100 cc.

2. **Ointments.**—Ointments, greases, or pomades are mixtures of fat or fatlike substances physically bound together, essentially free from water. They may contain other drugs or modifiers. They possess a melting point approximately the same as that of the skin. They adhere to the area, prevent evaporation, and are protective. They engender heat and cause congestion.

Ointment bases may be classified as follows: (a) EPIDERMIC ointment bases are intended to limit activity to the skin surface. Their ingredients include mineral oil, mineral waxes, or combinations.

(b) ENDODERMIC ointments are intended to produce activity by permitting the drug to penetrate into the skin. Lard and wool fat are two typical examples of bases of this type of ointments.

(c) DIADERMIC ointments are designed to assist passage of the medicament through the skin. Certain volatile oils are effective on application in a diadermic base ointment.

Hydrogenated fats, with all degrees of hydrogenation, are available commercially. These are useful ointment bases.

Cerates are combinations of fatty bases and waxes which are not soft enough to melt and run when applied to the skin.

Pastes are ointmentlike mixtures of powders with equal parts of glycerin, soft soap, petrolatum, lard, etc They are protective and

soften the skin; they are porous and tend to relieve congestion. *Bentonite* is a good carrier for chemical reducing action in pastes.

The following ointments are useful:

SULFUR OINTMENT

℞

Washed Sulfur	20 Gm.
Potassium Carbonate	10 Gm.
Water	10 cc.
Wool Fat	10 Gm.
Hydrogenated Oil qs.ad	90 Gm.

Dissolve potassium carbonate in water, incorporate with wool fat, mix with sulfur and hydrogenated oil.

SCALP POMADE

℞

Resorcinol Monoacetate	4 Gm.
Castor Oil	30 cc.
Sesame Oil	30 cc.
Cetyl Alcohol	2 Gm.
Ceresin	20 Gm.
Hydrogenated Oil Petrolatum āā q.s.ad	100 Gm.

3. **Protective Ointments** are used to protect the skin from irritants. These preparations must be nonirritating and nonsensitizing, be protective, and finally, easily applied and easily removed.

(a) SIMPLE VANISHING CREAM is an emulsion of stearic acid in water containing soap. The cream does not really vanish. After evaporation of the water, a thin, almost invisible, nongreasy layer remains which acts as an excellent foundation for application of powder. When rubbed into the skin, vanishing cream fills the pores with soap which facilitates removal of dirt.

℞

Stearic Acid	20 Gm.
Sodium Carbonate	2 Gm.
Glycerin	6 cc.
Water	78 cc.

(b) PROTECTIVE OINTMENTS AGAINST OILS, GREASES, PITCH, SUNLIGHT.—

℞

Anhydrous Lanolin	70 Gm.
Castor Oil	30 cc.
Perfume q.s.	

(c) DETOXIFYING PROTECTIVE OINTMENTS.—A cream designed to protect against alkalies may well contain boric or benzoic acid, intended to neutralize the alkalies. The presence of the fat or oil may further combine with the acid to form a soap. A protective cream against acids may contain soap and magnesium hydroxide. Any substance which may be detoxified by oxidation may contain a nonirritant oxidizer such as the various oxidizing peroxides, or one that gives off chlorine as dichloramine-T.

(d) PROTECTIVE OINTMENTS CONTAINING INERT POWDERS.—The powder may be calamine, zinc oxide, bentonite, etc. The adhesive may be gum benzoin and a vanishing cream.

℞

Zinc Oxide	5 Gm.
Talc	5 Gm.
Iron Oxide	1 Gm.
Gum Benzoin	2 Gm.
Vanishing Cream	60 Gm.
Alcohol	15 cc.
Water	10 cc.

(e) PROTECTIVE OINTMENTS AGAINST SUNLIGHT.—Rays of the sun which cause burning may be screened out by certain chemicals. These substances include methyl salicylate, aesculin, cycloform, methyl benzoate, benzyl salicylate, quinine oleate, tannates, and tannic acid.

℞

Lanolin	58 Gm.
Castor Oil	30 cc.
Titanium Dioxide	5 Gm.
Methyl Salicylate	5 cc.
Duponal	2 cc.
Perfume q.s.	

Note: Many combinations may be made by incorporating two or more of the ointments described.

PREPARATIONS

Lard, *Adeps*, U.S.P., B.P. The purified internal fat of the abdomen of the hog. Insoluble in water, and only slightly soluble in alcohol.

Benzoinated Lard, *Adeps Benzoinatus*, U.S.P., B.P. Somewhat antiseptic and less liable to become rancid than ordinary lard.

Hydrous Wool Fat, *Adeps Lanae Hydrosus*, U.S.P., B.P. (Lanolin). Wool fat with about 27 per cent of water.

Cerate, *Ceratum*, N.F. White wax (30%) and benzoinated lard.

Rosin Cerate, *Ceratum Resinae*, U.S.P. Rosin, yellow wax, and lard.

Petrolatum, *Petrolatum*, U.S.P. Paraffinum Liquidum, B.P. A purified semisolid mixture of hydrocarbons from petroleum. Insoluble in water and almost insoluble in alcohol.

White Ointment, *Unguentum Album*, U.S.P. (Simple Ointment). White petrolatum 90 per cent, wool fat 5 per cent, white wax 5 per cent.

Rose Water Ointment, *Unguentum Aquae Rosae*, U.S.P. Sodium borate (0.5%), spermaceti, white wax, almond oil, rose water, and rose oil.

Zinc Oxide Ointment, *Unguentum Zinci Oxidi*, U.S.P. Zinc oxide (20%), wool fat, and white petrolatum. B.P., 15 per cent ZnO.

D. Excipients

Excipients are substances of a more or less inert nature added to a prescription in order to confer a suitable consistency or form to the drug. Excipients may be liquid or solid substances.

1. Moist Excipients.—Included in this group are the glycerites (of acacia, starch, tragacanth), honey, simple syrup, and water.

2. **Solid Excipients.**—The common solid excipients are acacia, albumen (egg), starch, althea, glycyrrhiza, kaolin, lactose, petrolatum, and soap.

The choice of the excipient may be left to the pharmacist. For oxidizing substances, such as potassium permanganate, the diluent should be an inert powder, such as kaolin, and the excipient an inert substance, like petrolatum.

Pills intended to pass through the stomach unchanged, but to be dissolved in the intestine, are known as "enteric pills." These pills are coated with salol, keratin, stearic acid, hardened gelatin, etc. Pills may also be "chocolate coated" to improve their taste, appearance, and keeping qualities.

Propylene Glycol, N.F. Racemic propylene glycol, $CH_3CHOH.CH_2OH$, is used for pharmaceutic purposes as a diluent. Its toxicity is similar to that of glycerin. As ordinarily employed it may be considered practically nontoxic.

PREPARATIONS

Althea, *Althaea,* N.F. (Marsh Mallow Root).
Starch, *Amylum,* U.S.P., B.P. (Cornstarch).
Starch Glycerite, *Glyceritum Amyli,* U.S.P. Glycerinum Amyli, B.P. Starch (10%), distilled water (20%), benzoic acid and glycerin.
Glycyrrhiza, *Glycyrrhiza,* U.S.P., B.P. (Licorice Root). The preparations are incompatible with acids.
Kaolin, *Kaolinum,* N.F., B.P. Purified native hydrated aluminum silicate.
Lactose, *Lactosum,* U.S.P., B.P. Obtained from cow's milk.
Honey, *Mel,* N.F. Mel Depuratum, B.P.

INCOMPATIBILITY

The word "incompatibility" means that the ingredients are incapable of existing together in harmony. Thus a prescription is incompatible when its ingredients will produce one or more of the following changes: (1) decomposition; (2) precipitation; (3) liquefaction; (4) deterioration; (5) explosion; (6) antagonistic action; (7) or do anything that defeats the prescriber's intent.

Incompatible prescriptions result from carelessness or ignorance on the part of the prescriber. If the incompatibility is not corrected by the pharmacist, the therapeutic results desired may not be obtained or in some instances the mixture may prove harmful or even fatal to the patient.

In writing a prescription which contains more than one drug, one or more of the above-mentioned changes may result from the mixture, unless the prescriber exercises extreme care in considering the properties of the ingredients entering into the prescription. Four classes of incompatibility are of interest in prescription writing:

1. **Physical Incompatibility** occurs when there is a change in the physical state of one or more of the ingredients, such as precipitation, liquefaction or other undesirable physical change.

2. **Chemical Incompatibility** involves a chemical interaction between the ingredients. These changes may consist of the formation of new or dangerous compounds, or the destruction of some of the compounds added.

3. **Pharmaceutical Incompatibility** occurs when either a chemical or a physical change takes place, which, while not affecting its

therapeutic value, renders it unsuitable for administration because of its undesirable appearance, taste, or smell.

4. **Therapeutic Incompatibility** occurs when the constituents of a prescription produce antagonistic physiological actions when administered.

COMMON INCOMPATIBILITIES.—

Acacia is precipitated by alcohol, borax, and ferric chloride tincture.

Acids, unless very dilute and in small amounts, should be prescribed alone. They combine with bases to form salts, and are incompatible with oxides, alkalies, alkaline salts, hydrates, and carbonates. They usually precipitate albumin.

Alcohol in sufficient concentration precipitates gums, albumin, and many inorganic salts from their aqueous solution.

Alkalies and Alkaline Carbonates should rarely be prescribed in solution with other drugs. They form salts with acids and precipitate many metallic alkaloidal salts.

Alkaloidal Salts should rarely be combined with other drugs in solutions. They are precipitated by alkalies, alkaline carbonates, earthy carbonates, preparations containing tannic acid, and by iodides in solution. Any precipitation of alkaloids might result in the last dose of a bottle of medicine being a dangerous one.

Arsenic (arsenous acid, arsenic trioxide) should generally be prescribed in solution alone. It is precipitated by salts of iron, magnesia, and solutions of lime.

Bromides in solution should not be combined with alkaloids. They precipitate the salts of morphine, quinine, and strychnine from neutral solutions.

Chlorates and other oxidizing substances may cause an explosion when triturated dry with any of a number of organic substances which are readily oxidized.

Epinephrine is decomposed by alkalies, alkaline carbonates, and hydroxides.

Glucosides, e.g., glycyrrhizin, are destroyed by acids.

Iron Salts.—Ferric salts are precipitated from aqueous solutions by alkaline hydroxides and carbonates; they form a blue-black solution or precipitate with tannic or gallic acid; they form a violet color in dilute salicylate or phenol solutions. *Ferrous salts* give white precipitates with tannic acid and gallic acid, and these turn black on standing due to conversion into the ferric state.

Mercury Salts.—Mercuric salts precipitate alkaloids, glucosides, proteins, tannin, and antipyrine. Mercuric chloride forms a double salt with potassium iodide which is soluble in the excess of either of the original salts. (A common error is the administration of a mercurous preparation, especially to the eye, in a person who is taking iodides.) Mercury salts are often incompatible with other metals. The mercuric or mercurous salts of halogens form a black precipitate with the fixed alkaline hydroxides and with limewater.

Oils and Fats form soaps with alkaline hydroxides, metallic oxides and limewater.

Oxidizing Agents (nitrates, nitrites, manganese, chlorates, bromine, iodine, bromates, iodates, permanganates, etc.) may react violently with *reducing agents* (tannins, glycerin, sugar, alcohol, ether, sulfates, pyrogallol, arsenous acid, ferrous and mercurous salts, etc.).

Resins, including oleoresins, fluidextracts and tinctures containing resins, should not be prescribed in watery solutions, though they may be ordered in emulsions by suspending them with the mucilage of acacia or tragacanth. They are all precipitated by water.

Salicylates, Phenol, and Tannin precipitate or color iron salts. Tannin also precipitates most other metals, alkaloids, some glucosides, and neutral principles. Salicylates precipitate quinine.

Salts of Metals are precipitated by alkaloids, sulfides, tannin, and proteins. They precipitate some alkaloids and acacia. Mercuric salts are often incompatible with other metals. Silver and lead salts are precipitated by chlorides, bromides, and iodides. Silver salts are also incompatible with organic substances. Iron salts are colored by tannin, salicylate, and phenol.

Spirits should not be prescribed with watery preparations. They become cloudy on the addition of water.

Water should not be added to:

Alcoholic liquids in general (such as tinctures, spirits, fluidextracts, with some exceptions); or to ethereal liquids (oleoresins), or oils.

(Phenol should not be mixed with collodion.)

Prescribe Official Drugs

The modern physician will usually find a sufficient number of useful drugs in the United States Pharmacopoeia, National Formulary, or the New and Nonofficial Remedies. There is seldom need of prescribing proprietary preparations. The druggists can supply various preparations complying with official standards, which he purchases in bulk, and sells without a firm name. Usually the nonproprietary drugs will sell for less. When drugs are prepared and standardized according to the U.S.P. or N.F. there should be little choice of brands. The following table gives comparative costs of proprietary and Official Drugs.

COMPARATIVE COST PER 30 GRAMS

Proprietary		*Official*	
Adrenalin	$0.89	Epinephrine Solution	$0.60
Anesthesin	1.60	Ethyl Aminobenzoate	.55
Argyrol	1.50	Silver Protein	.52
Luminal	1.50	Phenobarbital	.30
Novocain	2.00	Procaine Hydrochloride	1.43
Phenacetin	.63	Acetophenetidin	.18
Pyramidon	.81	Aminopyrine	.47
Veronal	3.00	Barbital	.59

Safety Generalities in Prescribing

The medical student can hardly master the general field of incompatibility in the time allotted him; the following suggestions, however, may help him:

1. Prescribe simple drugs, the pharmacology of which is understood.
2. Retain a knowledge of the elementary chemical reactions.
3. Most vegetable drugs contain tannin which reacts with such substances as alkaloids and iron salts.
4. Avoid mixing acid-reacting drugs with substances having alkaline reaction unless the reaction is desired.

5. In general do not mix strong alcoholic solutions (tinctures, elixirs, fluidextracts) with water or aqueous preparations.

6. Prescribe the generally incompatible drugs alone (acids, alkalies, iodides, bromides, heavy metals, alkaloids, tannins, carbonates, salicylates, permanganates).

7. When in doubt about the solubility of a drug in the solvent used, increase solvent in the individual dose.

8. Learn a few compatible combinations. For example: Compound Sarsaparilla Syrup, U.S.P., is an excellent remedy to conceal the taste of salts and mercury, iodides, bromides, ammonium chloride, and sodium salicylate. Quinine sulfate may be well administered in Cacao Syrup, N.F.

9. The following substances are almost universally incompatible:

Strong Mineral Acids	Potassium Iodide
Strong Alkalies	Arsenic
Bichloride of Mercury	Tannic Acid
Silver Nitrate	Alkaloids
Lead Acetate	Metal Salts
Potassium Permanganate	

10. Confer frequently with your pharmacist.

11. The physician is legally responsible for any errors but the pharmacist is co-responsible if a prescription is filled for a fatal dose of a drug.

References

Arny, H. V.: Principles of Pharmacy, ed. 4, Philadelphia, 1937, W. B. Saunders Co.

Bethea, O. W.: Materia Medica, Drug Administration and Prescription Writing, ed. 5, Philadelphia, 1938, F. A. Davis Co.

Clark, A. J.: Individual Variation in the Response to Drugs, Tr. Med. Clin. Soc. Edinburgh **42**: 1-16, 1935; in Edinburgh M. J. (January) 1935.

Cooper, J. W.: Latin for Pharmaceutical Students, London, England, 1930, Sir Isaac Pitman & Sons, Ltd.

Eggleston, Cary: Essentials of Prescription writing, ed. 7. Philadelphia, 1942, W. B. Saunders Co.

Fantus, B.: General Technic of Medication, Chicago, Ill., 1930, American Medical Association.

Husa, Wm. J.: Pharmaceutical Dispensing, ed. 2, Easton, Pa., 1941, Mack Printing Co.

Jackson, D. E.: Experimental Pharmacology and Materia Medica, ed. 2, St. Louis, 1939, The C. V. Mosby Co.

Klumpp, T. G.: The New Federal Food, Drug and Cosmetic Act, J. A. M. A. **116**: 830, 1941.

Lyman, R. A.: (Editor) American Pharmacy, Philadelphia, Pa., 1945, J. B. Lippincott Co.

Muldoon, H. C.: Pharmaceutical Latin, ed. 3, New York, 1937, John Wiley and Sons.

Narcotic-Internal Revenue Regulations, 1938, Washington, D. C., U. S. Gov't Printing Office.

Prinz, Hermann: Pharmacology and Dental Therapeutics, ed. 9, St. Louis, 1945, The C. V. Mosby Co.

Purdum, W. A.: Method of Evaluating Relative Efficacy of Disguising Agents for Distasteful Drugs, J. Am. Pharm. A. **31**: 298 (Oct.), 1942.

Ruddiman and Nichols: Incompatibilities in Prescriptions, New York, 1936, John Wiley and Sons.

Scoville, W. L.: The Art of Compounding, ed. 5, Philadelphia, 1927, P. Blakiston's Son & Co. Revised by H. H. Powers, 1943.
Smith, C. S., and Wikoff, H. L.: Practical Materia Medica, Philadelphia, 1929, Lea and Febiger.
The British Pharmaceutical Codex, Fifth Supplement, 17 Bloomsbury Square, W.C.I., 1942, The Pharmaceutical Press.
The Food and Drug Administration, Federal Security Agency, Miscellaneous Publication No. 1, United States Government Printing Office, Washington, D. C., 1941 (Obtainable from Supt. of Documents, Washington, D.C., price 10c).
The National Formulary, ed. 8, 1947.
The Pharmacopoeia and the Physician, A. M. A., Chicago, 1936.
United States Dispensatory, ed. 24, Philadelphia, 1947, J. B. Lippincott Co.
United States Pharmacopoeia, Thirteenth Revision, 1947.

CHAPTER IV

TOXICOLOGY

General

This chapter will be devoted to a brief résumé of general and industrial toxicology. Certain matters of general application will be discussed, while details will be considered under the individual drugs. The importance of *industrial toxicology*, i.e., the knowledge of injurious actions of substances in industry, has been greatly enhanced during recent years.

Toxicology is the science of poisons. It deals with the origin, symptoms, diagnosis, treatment, and detection of poisons.

Definitions: It is almost impossible to define the term "poison," for substances which are dangerous under certain conditions are harmless in others. Peterson, Haines and Webster (1923) give us the following definition: *"A poison is a substance, which, when introduced into the body in relatively small quantity and acting chemically, is capable of producing death or serious injury to health in the case of an ordinary individual in average health."*

All drugs are potentially poisons and the separation of their pharmacological and toxicological properties is often difficult. The therapeutic and toxicologic doses of many drugs, for example, digitalis, are very close; with caffeine the doses are more widely separated; while with the vitamins the toxic doses may in some instances be several thousand times the therapeutic doses.

A *legal poison* is any substance which causes disease or death, given with homicidal intent.

Acute Poisoning.—Acute poisoning is the toxic manifestations produced by taking a large amount of a poison in a single dose, or several smaller doses with such frequency as to result in sudden illness.

Chronic Poisoning.—Chronic poisoning is the toxic manifestations following the taking of small doses of a poison over a long period of time. It results in the gradual but progressive deterioration of body function, e.g., mercury, lead, etc.

Cumulative Poisoning.—Cumulative poisoning is the toxic manifestations caused by a sudden increase in intensity of the action following slow additions of the drugs, e.g., digitalis.

ACTION OF POISONS

Poisons may cause injury or death by intense local action or by their action on remote organs after absorption, or by both means.

Local poisons exert their action on the mucous membranes of the alimentary canal. Certain poisons such as strong acids and alkalies cause intense tissue damage and usually produce a condition of shock similar to that produced by extensive burns on the surface of the body.

Many of the metallic poisons produce not only a local irritant action but also a toxic action after absorption. On the other hand, most alkaloidal poisons produce only a remote poisonous action following absorption, e.g., opium, strychnine, and others.

THE FATE OF POISONS

After absorption the drug circulates in the blood stream, coming in contact with every organ and tissue of the body. The toxic action of a drug is presumed to depend on the establishment of a toxic concentration in the blood stream or lymph around the various body organs.

When a drug is given orally, hypodermically, or by any other route, the concentration attained in the blood depends on its rate of absorption. After absorption the action of the drug is determined by its rate of excretion, its fixation by tissues, and its detoxication by such processes as oxidation, reduction or synthesis to some less toxic material. The rate of absorption, the storage of poisons in the tissues, their rate and modes of elimination are of great medico-legal interest.

Nonvolatile poisons are eliminated from the body chiefly by the kidneys; metals are excreted to a large extent in the colon, and a few alkaloids, such as morphine and emetine, are also excreted by this route. Small amounts of poisons may be eliminated from the body through the skin, and in the saliva. A certain quantity of poison is excreted by the bile into the duodenum, and re-excretion may take place into the intestine; for example, morphine is mostly excreted by the intestine. Arsenic may be found in the stomach of a dead person if death was caused by inhalation of arseniureted hydrogen fumes.

The liver is the chief organ that defends the body against noxious poisons such as drugs, and against complex substances formed during digestion and metabolism. If the drug is absorbed by the alimentary tract, it is conveyed by the portal vein to the liver which absorbs much of the poison, thus acting as the first line of defense. It detoxifies many substances and fixes other substances which it cannot detoxify. The liver fixes arsenical compounds as well as many other compounds and in doing this exposes itself to serious injury. Thus the liver bears the brunt of the attack when any drug or poison is introduced into the body, and in so protecting the body may undergo damage, such as cloudy swelling, fatty degeneration, or even necrosis.

It is well to know that the presence of glycogen in the liver cells increases its ability to resist poisons. It is therefore advisable to give a substantial amount of glucose within a few hours of the administration of a toxic drug, such as general anesthetics, arsenic, or benzol derivatives. In cases in which the liver has undergone necrosis and life persists for several days after the poison was taken, the cause of the death will likely be autointoxication from hypohepatic function and perhaps little or none of the poison will be found in the body.

The following examples are given to illustrate the fate of poisons in the body.

1. **Phenol.**—Phenol is a striking example of the several different ways in which a drug is acted upon in the body. A large part is oxidized to hydroquinone and pyrocatechin, both of which are excreted by the kidneys. A portion of the drug may be combined with sulfuric acid to form phenyl-sulfuric acid which is harmless. Some of the drug may unite with glycuronic acid and be eliminated by the kidneys.

2. **Carbon Monoxide.**—Carbon monoxide is eliminated unchanged and is not oxidized to carbon dioxide. The time required completely to eliminate this poison by respiring pure air is not known, but

varies with different persons, the carbon monoxide hemoglobin apparently not being in all cases under sufficient tension with oxygen to free readily the carbon monoxide. In fatal cases it persists for a long time in the blood and muscles.

3. **Methyl Alcohol.**—The fate of methyl alcohol is quite different from that of ethyl alcohol, for where ethyl alcohol is rapidly oxidized to carbon dioxide and water, methyl alcohol is slowly oxidized to formic acid and is excreted as formates. The excretion of formates lasts for five or six days after the administration of large doses of methyl alcohol.

4. **Mercury Bichloride.**—Mercury compounds are absorbed in the body regardless of the source of administration. A considerable amount is absorbed by the white cells and deposited in various organs, chiefly in the kidneys and liver. After absorption it leaves the blood rapidly; a part is excreted by the urine and feces. A trace of mercury is found in the bile, sweat, saliva, and the gastric and intestinal juices. Excretion occurs largely during the first week following administration, but traces are excreted intermittently for several months longer.

5. **Hydrocyanic Acid.**—Hydrocyanic acid is excreted, in part, unchanged, from the lungs, while some of it is converted into sulfocyanides and excreted in the urine. It has been suggested that it may combine the aldehyde group of the body sugar, or be hydrolyzed by ferments into ammonium formate.

SYMPTOMS OF POISONING.

A knowledge of the general symptoms of poisoning is invaluable in making a diagnosis of poisoning. The fate of the patient is often determined by the early recognition of these symptoms.

If symptoms of poisoning appear following a meal, food poisoning is suspected. Care must be exercised so as not to confuse the onset of disease with poisoning. Diseases are generally much slower in their progress, and are usually preceded by circumstances such as exposure, characteristic symptoms, and indisposition for several days. A knowledge of the following symptoms may aid the physician in diagnosing poisoning.

1. **Vomiting.**—Vomiting, frequently associated with purging and abdominal pain, is often found in the presence of gastrointestinal upset or with the onset of acute disease. Vomiting is caused by such common poisons as arsenic, antimony, digitalis, phosphorus, copper, iodine, mercury, the sulfonamides, etc. It is frequently associated with such diseases as gastritis, ulcer, uremia, acute infectious diseases, and brain tumors. The early stages of pregnancy are often associated with vomiting.

2. **Convulsions.**—Convulsions, or violent involuntary contractions of the voluntary muscles, are commonly associated with such diseases as epilepsy, uremia, eclampsia, many acute cerebrospinal disturbances, and tetanus. Poisoning by strychnine, nicotine, camphor, aspidium, picrotoxin, and cyanides cause convulsions.

3. **Coma.**—Coma may follow poisoning by such drugs as opium and its derivatives, chloroform, hypnotics, carbon dioxide, atropine, alcohols, and phenols. It is a common symptom of uremia, eclampsia, acidosis, diabetes, and of many brain lesions.

4. **Respiration.**—Dyspnea is a common symptom of respiratory poisoning. Edema of the glottis, muscle spasm, and the action of respiratory depressants may produce dyspnea. Slow respiration is produced by opium and its derivatives and by carbon monoxide,

while rapid respiration may be caused by such drugs as atropine and carbon dioxide. Slow respiration is caused by such conditions as uremia, hemorrhage, and compression of the brain, while rapid respiration is commonly associated with acute respiratory diseases, hysteria, and lesions of the medulla oblongata.

5. **Delirium.**—Delirium may be associated with poisoning by drugs of the atropine group, cocaine, cannabis, and alcohol. This condition is commonly found in epilepsy, insanity, delirium tremens, nephritis, and with certain organic brain diseases.

6. **Dilatation of Pupil.**—Many drugs, such as the drugs of the atropine group, cocaine, and nicotine, produce mydriasis. Certain nervous diseases causing optic atrophy and irritation of the sympathetic system usually cause dilatation of the pupil.

7. **Contraction of Pupil.**—Pin-point pupils are characteristic of poisoning by members of the opium group; by drugs that stimulate the parasympathetic nerves, such as pilocarpine, physostigmine; by chloral, phenol, etc. Contraction of the pupil is characteristic of tabes dorsalis.

8. **Paralysis.**—Paralysis may follow poisoning by cyanides, carbon monoxide, and carbon dioxide. Botulism is characterized by paralysis. Common diseases accompanied by various degrees of paralysis are apoplexy, meningitis, tabes, and poliomyelitis. Thrombosis of the cerebral vessels may result in paralysis.

9. **Cyanosis.**—Cyanosis is often an indication of nitrobenzene, aniline, or acetanilid poisoning. Opium derivatives and the sulfonamide drugs often produce this symptom. Many cardiac and respiratory diseases and brain lesions are accompanied by cyanosis.

10. **Salivation.**—Salivation is an early symptom of mercury poisoning. Pilocarpine and other stimulants of the parasympathetic nervous system produce salivation.

11. **Odor of Breath.**—The odor of the breath may be a means of detecting a toxic condition. A diabetic in coma may elicit an acetone breath; hydrocyanic poisoning is characterized by an odor of almonds, while phosphorus produces a garlicky breath. Other substances, such as alcohol, ammonia, bromine, paraldehyde, iodine, etc., cause characteristic breath odors.

12. **External Tissue Destruction.**—By the careful examination of signs of external tissue destruction clues may be found indicative of the poison ingested. For example, yellow stains about the lips may indicate nitric acid poisoning, signs of escharing about the lips and mouth may be caused by sulfuric acid, while greenish-blue discoloration of the tongue and mucous membranes of the mouth could result from ingestion of Paris green or other copper salts.

CONDITIONS THAT MODIFY THE EFFECTS OF POISONS

The poisonous effects of drugs are modified by certain conditions which in general modify all drug action. The conditions which particularly modify the poisonous effects of drugs include the following:

1. **Dose.**—Generally, the larger the dose the more rapid is the action; furthermore, a large dose may produce shock symptoms before the appearance of the typical symptoms.

The fatal dose of a drug for man, obviously, is difficult to determine. Experimental data on animals, and recorded cases of death from known amounts of poison give very inaccurate information and should be considered merely an approximation.

2. **Rate of Absorption.**—The rate of absorption of a drug is an important factor in determining its poisonous action. The rate of absorption depends on its form, whether soluble, insoluble, gaseous, or liquid. A poison must be in soluble form to exert true poisonous effects. A poison in a gaseous state is more readily absorbed by the lungs than is a poison in a solid or liquid state.

The genitourinary tract has been a frequent place of absorption of poisons. A number of cases of mercurial poisoning have been due to the use of bichloride of mercury solutions in vaginal douches.

3. **Route of Administration.**—Symptoms of poisoning usually appear most rapidly when the poisons are administered by channels that carry the material most rapidly to the blood stream. The routes of administration usually facilitating the quickest drug action are listed in order of speed of action as follows: intravenous, inhalation, intraperitoneal, intramuscular, subcutaneous, and oral. Food in the stomach may delay poisonous action; gastric enzymes may destroy certain poisons. Certain toxic materials, such as snake venom, some bacterial toxins, etc., are harmless when taken orally but are dangerous poisons when administered hypodermically. Conversely, the glucoside, amygdalin, if administered by vein is harmless, but when given orally is a dangerous poison. Magnesium sulfate when given by vein is a dangerous depressant, but is harmless when taken orally.

4. **Habit and Tolerance.**—The body has the ability to become accustomed to the use of drugs and acquires the property of withstanding large doses of some drugs without showing toxic symptoms which would be present if the body had had no previous contact with the drug. This is well illustrated in morphine or cocaine addicts. After repeated administration the body acquires a tolerance to these drugs, so that much larger doses are necessary to produce the same effects as were produced initially.

5. **Disease.**—Disease is an important factor in determining the action of drugs or poisons. Some diseases seem to bring about a tolerance for certain poisons while other diseases cause a hypersensitivity to their action. A morphine tolerance seems to be present in cases of intense pain. Any disease affecting the organs or routes of elimination accentuates the poisonous action of drugs. For example, if a drug is eliminated in the urine, disease of the kidney retarding urine elimination may increase the toxic manifestations. Any impairment of the general health of the body tends to decrease the ability of the body to offset the effect of poisons.

6. **Idiosyncrasy.**—Idiosyncrasy may be defined as an individual hypersensitivity to the action of a drug. Some persons may react normally to a drug with excellent therapeutic manifestations, while others will react to the drug as though it were a violent poison, e.g., quinine.

7. **Speed of Administration.**—The rapidity with which a drug is administered may determine whether its action will be beneficial or toxic. The ill effects of salvarsan may be due to too rapid injection. Quinine if administered too rapidly by vein may cause heart failure. It is advisable to administer intravenous drugs very slowly and in dilute concentration so as not to upset the colloidal equilibrium of the blood.

8. **Age.**—Susceptibility to drugs generally increases in old age. Children, as a rule, are more susceptible to narcotics than adults. On the other hand, atropine and calomel are better tolerated by children than by adults.

It is well to remember that any conditions which modify the effects of drugs modify the effects of poisons.

DUTIES OF PHYSICIAN IN POISONING CASES

Obviously, the first duty of the physician is to restore the patient to health. This usually requires removal of the poison, the administration of a suitable antidote, and the treatment of the symptoms. The physician has another duty to the State, namely, he should preserve any evidence which may prove of special value in establishing cause of the poisoning and any circumstances associated with the poisoning.

The symptoms must be carefully observed and *recorded.* The exact time the physician was called, the order and time of appearance of symptoms, odor of the breath, the condition of the pupils, the character of the pulse and respiration. The occurrence of convulsions, paralysis, delirium, etc., all should be carefully recorded. He should record all treatment given.

The physician must personally see that the stomach contents, washes, vomitus, feces, or other fluids are placed in clean glass jars, wrapped, and properly sealed. In case of autopsy, the stomach and its contents, the intestines, and portions of various vital organs should also be placed in clean jars and sealed. No antiseptics should be added. All samples should be placed in the refrigerator and locked so no possibility of tampering can occur.

DIAGNOSIS OF POISONING

The diagnosis of poisoning before death is often easy, sometimes difficult, and occasionally impossible. When one considers the large number of poisons available, their variability in action depending on size of dose and conditions under which they may be taken, and that there are many diseases that simulate poisoning, then one realizes the complexity of the problem. A higher percentage of correct diagnoses could be made, however, if a few general principles were followed. The following means are employed to diagnose a case of poisoning.

The first important step in the investigation of a suspected fatal poisoning is a thorough examination of the location where the body was found. An intensive search should be made for containers from which the deceased may have taken the poison, such as cups, bottles, jars, etc. All food found on the premises should be confiscated for chemical analysis.

1. **History.**—An accurate history is indispensable in making a diagnosis of poisoning. A written record of all observations should be made, and an accurate history of the case should be obtained from the patient, relatives or friends. No detail should be considered too trivial to record for later reference.

Don't mistake poisoning for a disease. If the patient has been in good health and suddenly becomes ill, think of poisoning. Sudden illness following a meal favors a diagnosis of poisoning. A differential diagnosis between poisoning and an acute disease may be difficult to make. Certain diseases that may simulate acute poisoning are: acute gastrointestinal disorders, appendicitis, intestinal strangulation, ruptured tubal pregnancy, coma associated with infectious diseases and many more.

2. **Symptoms.**—A knowledge of the general symptoms following poisoning are indispensable to a physician in arriving at a correct diagnosis for a case of poisoning. A record of the symptoms and signs associated with any particular poison case is a great aid to the toxicologist in making the examination for the offending drug. If a record of convulsions is sent in, with the sample to be analyzed, the toxicologist will think of strychnine and will immediately make a qualitative test for the presence of strychnine. *If one poison is found a second poison is rarely present* and no search is usually made by the toxicologist for the presence of another.

It is well to remember that *only a few clinical symptoms are sufficiently pathognomonic to be employed as diagnostic criteria.* However, a cherry red coloration of the blood indicates carbon monoxide poisoning; a brownish discoloration of the blood produced by the formation of methemoglobin points to poisoning by some such drug as nitrobenzene, acetanilid, or potassium chlorate. Poisonous symptoms are valuable chiefly as confirmatory evidence to be considered as part of the mass of evidence available from which a final diagnosis must be made.

3. **Physical Examination.**—A thorough physical examination should be made at once in a case of poisoning. The condition of the vital organs is of primary importance and, if necessary, the proper respiratory or circulatory stimulants should be administered. A neurological examination, with special emphasis placed on the reflexes, pupillary reactions, muscle tremors and psychic reactions, is of primary importance. Such an examination should be performed at frequent intervals to follow the course of the treatment instituted.

4. **Clinical Laboratory Examination.**—A chemical analysis of the urine, gastric contents, blood, and feces should be made as soon as possible after the patient has passed the emergency stage. Such analyses will do much to confirm the clinical diagnosis.

5. **The Post-mortem Examination (Necropsy).**—An examination of the dead body should be made to establish the previous diagnosis made on the case. Such an examination would eliminate the chance of mistaking natural diseased processes for poisoning. Following the autopsy the parenchymatous organs and contents of the hollow viscera should be taken for toxicological examination. *No preservative should be added; refrigeration should be used.*

6. **Toxicological or Chemical Analysis.**—A careful chemical analysis should be made of the organs and excretions of the body in order to determine the presence or absence of any poisonous agent. This is a specialty that is out of the field of the general practitioner or the commercial chemist. *The physician, however, should have a knowledge of the principles involved in toxicological analyses. He should have a practical knowledge of a few general tests.*

SOURCES OF ACUTE POISONING

A knowledge of the common sources of acute poisoning plus a knowledge of the usual contents of the more common of these is helpful in making a diagnosis. The ingredients of commonly used preparations are listed.

A. Patent Medicines

1. Laxatives—calomel, phenolphthalein, strychnine, belladonna, aloes.
2. Cold Cures—quinine, phenacetin, acetanilid, antipyrine, salicylates.

3. Ointments—camphor, phenol, quinine, turpentine, salicylic acid.
4. Liniments—alcohol, capsicum, chloroform, menthol.
5. Soothing Syrups—opium and its derivatives, calomel.

B. **Insecticides, Rat Poisons**

1. Fly Poison—arsenic.
2. Insect Powder—pyrethrum, sodium fluoride, lead, sulfur, lime, phosphorus, Paris green (acetoarsenite of copper).
3. Moth Poisons—camphor, naphthalene, cedar gum.
4. Ant Paste—arsenic trioxide, calcium arsenate.
   Ant Powder—sodium fluoride.
5. Roach Poison—sodium fluoride.
6. Termite Poison—para- or orthodichlorobenzene.
7. Rat Poisons—arsenic, lead, copper, sulfur, nicotine, strychnine, phosphorus, barium sulfate, red squill.

C. **Miscellaneous Household Poisons**

1. Bitter Almond—yields hydrocyanic acid.
2. Bordeaux Mixture—copper hydroxide.
3. Castor Beans—ricin.
4. Cream of Tartar—potassium acid tartrate.
5. Hair Dyes—paraphenylenediamine, pyrogallol, silver ammonium nitrate.
6. Lye—sodium hydroxide.
7. Mushrooms—muscarine and other toxins.
8. Obesity Cures—thyroid, dinitrophenol, dinitrocresol.
9. Red Precipitate—red oxide of mercury.
10. Saltpeter—potassium nitrate.
11. White Precipitate—ammoniated mercury.

TREATMENT OF POISONING

General Measures

If called to a case of poisoning, the physician should go immediately, taking his emergency bag with him. Time is important and a simple stomach wash may be better than the most elaborate hospital treatment at a later date.

On arrival, the room should be cleared and a rapid preliminary examination arrived at from the symptoms and appearance of the victim or presence of poison in a cup or bottle near him.

The principles of treatment are: *removal of poison* as thoroughly as possible, *neutralization of poison* to prevent further absorption, and treatment of symptoms by *supportive measures.*

It is well to remember, *when confronted with a case of poisoning of unknown origin, that there are general methods of treatment to be used which are usually more important than are specific antidotes.* The physician should be thoroughly familiar with the general rules applicable to the treatment of poisons.

Removal of Poison

In cases of poisoning, whether diagnosed or not, the stomach should be emptied by a stomach tube except in poisoning by strong corrosives.

It is well to get rid of solid matter by emesis before passing the tube, otherwise it is liable to become blocked. The following emetics

are used: powdered mustard—a dessertspoonful in a glass of warm water; sodium chloride 15 Gm. (4 drams) in a glass of warm water; copper sulfate—25 to 50 c.c. (⅝ to 1⅔ fluidounces) of 1% solution; zinc sulfate—2 Gm. in warm water; apomorphine hydrochloride—8 mg. (⅛ grain) subcutaneously is very valuable, but often fails in narcotic poisoning.

If vomiting has already occurred, it is obviously unnecessary to give an emetic, and if the patient is unconscious, an emetic, of course, cannot be given.

Lavage.—Gastric lavage should be undertaken even when emesis appears to have emptied the stomach. If a stomach tube is not available, a piece of rubber tubing 3 to 4 feet long, filled with a funnel at one end, may be used. Lubricate tube with glycerin or petrolatum, and pass one end well back in pharynx and into the esophagus. Ask the patient to swallow; however, if he is unconscious, the tube should be guided into the esophagus by putting the finger well back over the base of the tongue. Pass at least 20 inches of the tube in this manner. Next, raise the funnel well over level of the stomach and run in a pint of warm water. When funnel is nearly empty, pinch tube below junction of funnel and tube, and lower below level of stomach and siphon into a container. Save first washings of stomach for analysis. Repeat process several times, using at least two quarts of water. Appropriate antidotes may be introduced by the tube, but it is well to use warm water first and keep the fluid for analysis, before using any antidote.

Purgation.—Rapid purgation, using 50 Gm. (1⅔ ounces) of magnesium sulfate in a glass of warm water, may be indicated. Removal of poison from the intestine is facilitated by washing out the lower bowel.

Elimination of absorbed poison is aided by stimulating the kidneys with diuretics, by application of hot packs to the skin, and by transfusion with saline.

Neutralization of Poisons

No substance, as far as we know, can render a poison inert after absorption, but antidotal measures may be used to inactivate the poison. The method and antidote used depends on the type of poison.

Certain substances are physiologically antagonistic to one another, e.g., atropine and pilocarpine. In other instances, one drug controls or diminishes the effect of another, e.g., spasms of strychnine can be diminished by chloroform or barbital. The poison may be diluted by administering a quart of warm water. A quantity of animal charcoal suspended in water may be administered as a routine measure. It *adsorbs* a number of potent poisons.

A solution of potassium permanganate should be used for all oxidizable poisons, e.g., alkaloids, antipyrine, phosphorus, cyanides, and others. There is some difference of opinion as to the amount of potassium permanganate to use—500 cc. (1 pint) of a 1:1,000 solution is recommended. A weak solution of iodine, 15 drops of the tincture to a glass of water, may be used as an alternative to the permanganate.

Egg albumin may be used to protect the walls of the stomach and to precipitate the poison. Tannic acid (250 cc., or ½ pint, of 1 per cent), or strong tea (500 cc. or 1 pint), is useful as it causes protein precipitation and also the precipitation of some poisons.

"Universal" Antidote.—**There is no universal antidote but the following is an excellent general antidote for emergencies:**

℞

Saturated solution of iron sulfate	100 parts
Magnesium oxide	90 parts
Charcoal	50 parts
Water	900 parts

Mix all ingredients when ready to administer. This antidote is effective against arsenic, zinc, mercury, morphine, and strychnine.

"Special" Antidotes.—

For Arsenic	BAL
For Morphine	Potassium permanganate.
For Iodine	Starch solution, orally.
For Phosphorus	Copper sulfate, liquid petrolatum.
For Nicotine	Potassium permanganate (1:1,000) by gastric lavage. Caffeine and sodium benzoate (0.5 Gm.) intramuscularly.
For Wood Alcohol	Iodides, apomorphine.
For Strychnine	Potassium permanganate by stomach lavage. Soluble barbital by vein.

Supportive Measures

After the stomach has been washed out and the appropriate antidotes administered, attention must be given to symptomatic treatment. In some instances, supportive measures should be given the minute the doctor sees the patient.

Depression or Collapse.—Stimulants such as aromatic ammonia spirit 2 cc. (30 minims), in a half glass of water, or a hypodermic injection of caffeine and sodium benzoate 5 Gm. (7½ grains) are indicated in cases of depression or collapse.

In some cases, accompanied by vomiting and diarrhea, saline fluids are indicated. Administer 500 to 1,000 cc. (1-2 pints) of physiological saline, or 5 per cent dextrose solution, by vein.

In narcotic poisoning, especially by barbiturates, picrotoxin is of great value.

Heart and Respiration.—If breathing stops, artificial respiration should be given. In some cases of asphyxia, oxygen or oxygen with 7 per cent carbon dioxide may be necessary. If the heart stops, 1 cc. (15 minims) of 1:1,000 epinephrine solution may be injected directly into the heart.

Excitement and Convulsions.—If the patient is stimulated or excited, or in convulsions, he may be quieted by the use of chloroform or by a barbiturate. Chloral hydrate, 0.5 Gm. (7½ grains), sodium amytal, 0.2 Gm. (3 grains), or paraldehyde, 5-20 cc. (1¼ to 5 fluidrams) may be administered orally. Sodium amytal, 0.3 Gm. (5 grains), or sodium barbital, 0.3 Gm. (5 grains) may be given intravenously.

THE ANTIDOTE BAG

Every physician should keep the following antidotes together in an easily accessible place and in a special "Antidote Bag." The dose and route of administration should be printed on each container. In addition to these antidotes other materials of special importance

which should be kept in this bag are: hypodermic syringes, stomach tube and funnels, catheter, fountain syringe, and tongue forceps.

DRUG	DOSE	ROUTE
Amyl Nitrite Pearls	1 ampule	Inhalation
Apomorphine Tablets	2-8 mg.	Intramuscularly
Aromatic Ammonia Spirits	2 cc.	Orally
Atropine Tablets	1-5 mg.	Intramuscularly
BAL (dimercaptopropanol)	3 mg./Kg.	Intramuscularly
Butesin Picrate	q.s.	Externally
Caffeine and Sodium Benzoate	ampules (0.5 Gm.)	Intramuscularly
Calcium Gluconate	1 Gm.	Intravenously
Charcoal (animal, powdered)	1-2 Tablespoonfuls	Orally
Chloroform	q.s.	Inhalation
Cocaine Hydrochloride Tablets	0.03 Gm.	Hypodermically
Cupric Sulfate (powdered)	0.30 Gm.	Orally
Epinephrine Tablets	1 mg.	Hypodermically
Iron Sulfate (sat. sol.)	q.s.	Orally
Limewater	15 cc.	Orally
Magnesium Oxide	3 Gm.	Orally
Magnesium Sulfate	50 Gm. (500 cc.—10%)	Orally
Morphine Sulfate Tablets	10 mg.	Hypodermically
Olive Oil	30 cc.	Orally
Potassium Permanganate (1% sol.)	q.s. (dil. to 0.1%)	Orally
Sodium Sulfate	10 Gm.	Orally
Sodium Thiosulfate	1-10 Gm.	Orally
	20 cc. of fresh 5% filtered solution	Intravenously
Soluble Barbital	1 Gm. (20 cc. of 5%)	Hypodermically
Solution of Hydrogen Peroxide	3 cc. (dil.)	Orally
Strophanthin	5 mg.	Hypodermically
Strychnine Sulfate Tablets	2 mg.	Hypodermically
Syrup of Ipecac	7 cc.	Orally
Tannic Acid	1-5 Gm.	Orally
Tincture of Iodine	q.s.	Orally; externally

Physiological antidotes should be given hypodermically or intravenously in order to secure prompt and certain action, and to prevent loss of the antidote by vomiting. If the patient is seriously ill, treat him symptomatically (artificial respiration, heat) and then administer chemical antidote, followed by lavage of the stomach. Remember that the patient must be kept warm by blankets and by the application of dry heat.

INDUSTRIAL TOXICOLOGY

Industrial toxicology, or a knowledge of the injurious actions of substances used in industry, has always been important. Recently, however, with the many advances and changes in industry, this branch of medicine has taken on increased importance.

Medical supervision, especially in the larger plants, has almost eradicated occupational diseases. The introduction of new processes

and substances in industry, foreign to the medical profession, is a constant threat to the health of workers if constant medical supervision is not maintained at all times.

Industrial toxicology differs from general toxicology or ordinary poisoning in the following ways:

1. Path of entry of poisons is different.
2. Ordinary poisoning is usually acute while industrial poisoning is usually chronic.
3. Ordinary poisoning usually deals with a single poison while industrial poisoning is usually associated with more than one poison.
4. Environmental factors in industry may favor poisoning.

The path of entry in ordinary poisoning is usually through the mouth. In industrial toxicology, poisoning through the mouth rarely occurs. It is possible that men working with white lead, white arsenic, or Paris green may become poisoned if they allow their hands to contaminate their food, but such cases are rare.

Skin absorption of coal tar derivatives, aniline, the phenols, toluene compounds, and nitrobenzene compounds are of great importance. Skin absorption may also take place with members of the petroleum series, methyl alcohol, carbon tetrachloride, and others.

The respiratory tract is a source of entry of many industrial poisons. The upper respiratory passages, and even the entire lung tissue, may be irritated and also damaged by fumes from the heavy acids, by nitrogen oxides and by sulfur dioxide. Carbon monoxide, carbon dioxide, hydrogen sulfide, hydrogen cyanide, and certain petroleum distillates and derivatives may enter through the lungs without causing local irritation, then pass to the blood, causing great damage.

Mercurial poisoning may be caused by inhalation of mercury which volatilizes at room temperature. Hydrogen arsenate, a most dangerous form of arsenic, is given off when heavy acids come in contact with arsenic-bearing zinc or iron.

Inspired air may contain metal fumes or finely divided particles of sublimed oxides formed by heated metals.

Chronic poisoning in industry is far more common than acute. Chronic benzene poisoning occurs with much greater frequency than the acute form. Chronic mercury poisoning, chronic carbon disulfide poisoning, and many more, are also more common than the acute.

In ordinary toxicology a single poison is generally the offender. In a case of nonindustrial poisoning, if a single poison is detected the toxicologist looks no further for poisonous substances. On the other hand, in industrial toxicology, many toxic substances may be present and they may cause a complex and confusing picture. For example, printers use type containing lead and antimony and poisoning from these substances could hardly be diagnosed as a pure lead or as pure antimony poisoning. Many industries use a variety of volatile substances at once, which present a puzzling picture when toxic symptoms arise among the workmen.

The environment of the worker may be a factor contributing to industrial poisoning. This plays little part in nonindustrial toxicology. For example, factors that lower bodily resistance, heat, humidity, and fatigue may favor the action of poisonous substances. The proximity to various toxic substances of some workmen are obviously more common in indsutry. The varying susceptibility of workers to industrial poisoning has been a troublesome factor in solving many problems in industrial toxicology.

Treatment of Industrial Poisoning

Practically all poisoning occurring in industry can be controlled and their occurrence prevented. When a physician is called, in an instance of industrial poisoning, he should determine quickly the cause. In making the diagnosis he should contact the plant manager, or general superintendent, in order to locate the exact nature of the exposure.

The treatment of conditions resulting from noxious substances in industry is rarely specific, as several systems of the body are usually affected by the chronic exposure. Industrial substances, especially the solvents, usually affect the hemapoietic system, the nervous system, the kidneys, and often the liver.

Many gases and solutions have a strong affinity for hemoglobin and are also often destructive to the blood cells. For example, benzol may cause anemia. Arsine, and carbon monoxide are rapidly fatal due to their affinity for hemoglobin.

Solvents, so common in industry, usually cause disturbances of the nervous system. Their toxic action is, as a rule, due to their fat solvent action. They probably act on the fatty substances in the nerve fibers or myelin sheaths. Exposure to these solvents may produce narcotic effects and even death.

The kidneys may be damaged by excreting certain toxic substances e.g., carbon tetrachloride. The liver may be damaged by constant contact with such substances as carbon tetrachloride, the chlorinated naphthalenes, and others.

COMMON INDUSTRIAL POISONS

Inorganic Acids

SULFURIC ACID is very important commercially and rarely causes injury to workmen. Accidents may, however, occur among those who use it in their work. *Sulfur dioxide* is formed in many industrial processes, e.g., smelting of sulfide ores, production of sulfuric acid and phenol, bleaching paper, refrigeration, and others. It seems that workers become accustomed to sulfur dioxide, whereas persons unaccustomed to it react with choking in an atmosphere containing it. An atmosphere containing dangerous amounts of this gas produces bronchitis, bronchopneumonia, and edema.

Chronic poisoning from sulfur dioxide rarely occurs. Chronic exposure to this gas produces a mild nasopharyngitis, increased fatigue, abnormal reflexes, and dyspnea on exertion.

Treatment of Respiratory Disturbances.—Gas inhalations of oxygen plus 5 to 7 per cent carbon dioxide are indicated in persons overcome by sulfur dioxide. Use oxygen alone if pulmonary edema is present. Artificial respiration may also be indicated. Respiratory and circulatory stimulants such as metrazol and caffeine and sodium benzoate may be used. Bed rest may be necessary. Treat symptomatically.

Acute Poisoning may be caused accidentally or the acid may be taken for suicidal purposes.

Symptoms.—Onset is immediate, with severe burning pain in throat and stomach; coffee-grounds vomitus, purging, and profuse perspiration are common. Respiration becomes difficult. Acute edema of the larynx may cause death from asphyxia. Gradual weakness ensues, followed finally by shock and collapse. Death may occur in twelve to twenty-four hours.

External Treatment.—Flood with water, then cover with a paste of sodium bicarbonate. Wash eyes with 1 per cent sodium bicarbonate solution. Internal: Neutralize acid with aluminum hydroxide gel, 60 cc. (2 fluidounces); milk of magnesia (magnesia magma) 60 cc. (2 fluidounces); or 200 cc. (6⅔ fluidounces of calcium hydroxide [lime-water]). *Do not use stomach tube or emetics owing to danger of perforation.* Avoid sodium bicarbonate because of gastric distention from gas formed. Give white of egg, 60 cc. (2 fluidounces), or olive oil, 200 cc. (6⅔ fluidounces), for their demulcent and emollient action. Apply external heat. The pain should be controlled by injections of morphine. Intravenous saline may be of value.

HYDROCHLORIC ACID AND CHLORINE. Hydrochloric acid produces little industrial trouble, but *chlorine* is especially troublesome. Usually chlorine produces inflammation and a burning feeling in the throat. In severe cases lung edema may result. Few severe cases of poisoning, however, occur in industry.

Treatment.—Remove patient to fresh air, loosen clothing about the neck, and keep him warm. Administer oxygen in all cases. In severe cases venesection of from 400 to 600 cc. is indicated and should be performed early. This procedure often prevents development of edema of the lungs. The administration by vein of 10 per cent dextrose in physiological saline following venesection may be indicated to combat shock. Morphine sulfate, for relief of pain and excitement, may be administered early but with due precaution. It is contraindicated in the presence of pulmonary edema and respiratory difficulty.

Oxygen therapy is indicated if pneumonia occurs. Sulfa drugs are indicated if a specific infection occurs in the injured lung. Excess coughing may be controlled with codeine phosphate.

Acute poisoning produces symptoms similar to those of sulfuric acid, but differs in being less destructive. Hydrochloric acid is also volatile and more liable to attack the respiratory passages.

NITRIC ACID AND OXIDES OF NITROGEN. The manufacture of nitric acid and its use in industry is of toxicological significance. Nitric acid escaping in the air results in the formation of toxic nitrous and nitric oxide fumes. These fumes are irritating and caustic to the membranes of the respiratory tract.

Nitric acid is difficult to retain because of its extreme caustic action on substances. The acid is used in many industries, including manufacture of high explosives, nitrocellulose for celluloid, photographic films, lacquers, etc. Nitrous fumes are produced in welding under the intense heat of oxyacetylene or electric torch.

The oxides of nitrogen are extremely caustic on the respiratory tract. They produce a congestion of the throat, often edema of the glottis, and bronchial congestion. Edema of the lungs may result, followed by death. Pneumonia may develop. In exposure to large quantities death may occur rapidly and the only autopsy finding may be nitric acid in the blood.

Treatment.—Administer oxygen. McNally recommends passing the oxygen through ammonium carbonate (2 Gm. to 1.5 ounces of water) then into each nostril by means of an intranasal tube. Administer intravenously 50 to 100 cc. of 50 per cent dextrose twice daily, for relief of pulmonary edema. Sedatives may be given if necessary. If pneumonia occurs, treat with sulfa drugs.

Persons affected by chronic exposure may be aided by intravenous salyrgan. Restlessness may be treated by sedatives such as sodium bromide, phenobarbital, or pentobarbital. Treat any symptoms that may arise.

Acute Poisoning.—The symptoms produced are similar to those in sulfuric acid poisoning. There is no tendency to char the tissues, and therefore perforation occurs less frequently. Inhalation of fumes is more prone to cause inflammation and edema of the lungs. *Treat* as for sulfuric acid.

Hydrogen Fluoride and the Fluorides

Hydrogen fluoride, a very caustic acid, is used in frosting electric light bulbs, preparing metal for coating, for cleaning sandstone and marble, frosting glass, and removing porcelain enamel. Recently it has been used as a catalyst in the manufacture of high octane aviation fuel. *Fluorides* are used in smelting steel and aluminum and are given off in the production of superphosphate from phosphate rocks. Poisoning often occurs in the recovery of aluminum from cryolite, a double fluoride of sodium and aluminum with about 54 per cent fluorine. Acute poisoning may result from the accidental ingestion of sodium fluoride, a common constituent of rat and roach poisons.

Chronic fluorosis is characterized by mottled enamel of the teeth, osteosclerosis, and osteomalacia. Anorexia, loss of weight, cachexia, and anemia often are present.

Treatment.—In acute poisoning, lavage with limewater or a weak solution of calcium chloride. Administer 10 to 20 cc. of 10 per cent calcium gluconate by vein, one to three times daily. The calcium tends to counteract the calcium deprivation caused by the fluorine.

If cyanosis is present, administer oxygen intranasally. Respiratory and circulatory stimulants may be indicated, such as 7 per cent carbon dioxide in oxygen by inhalation, metrazol (0.1 to 0.3 Gm.) intramuscularly.

Codeine phosphate (30 to 60 mg.), repeated every four to six hours may be indicated in coughing. Ephedrine sulfate (24 mg.) may be useful if symptoms of bronchial asthma appear. Burned areas may be treated with a saturated solution of sodium bicarbonate. Suitable ointments may be indicated.

Alkalies

The alkalies used in industry are numerous. They include potassium and sodium hydroxide, sodium carbonate, and others. All of them produce a more or less caustic action on the skin but present no great problem in well-organized plants. *Ammonia*, being a gas, is more of a problem in industry. Leaks and breaks in refrigeration plants, storage battery manufacture, and rubber vulcanization may be common sources of ammonia poisoning.

Acute Poisoning. Symptoms.—The effects of the caustic alkalies (KOH, NaOH) are similar to corrosive acids. Their action is due to rapid absorption of water from the tissues, and to combination with fat and protein. Burning pain from mouth to stomach, difficulty in swallowing, tissue destruction, vomiting, and purging of blood and mucous are common symptoms. Cold clammy skin, dyspnea, feeble pulse, convulsion, and coma may soon follow. Delayed perforation or stricture may occur. For acute ammonia poisoning the symptoms are similar to those described; in addition, a certain amount of the gas is inhaled, causing inflammation and edema of the respiratory passages.

Treatment.—Flood water over external burns and then wash with vinegar. Wash eyes with a saturated boric acid solution. When taken

internally, neutralize with vinegar, 100 cc. (3½ fluidounces) or hydrochloric acid, 100 cc. (3½ fluidounces of 0.5 per cent). Olive oil, white of egg, and demulcent drinks are indicated. Caution: *Do not use stomach tube or emetics.*

Lead

Lead is of interest primarily because of its toxicological properties. It is looked upon universally as the industrial poison of greatest significance. The toxic action of lead was recognized by Hippocrates, who described a severe attack in a man who worked with metals. The syndrome of lead poisoning was fully described by Discorides in the first century A.D. The first record of experimental investigations on lead occurred in a treatise on toxicology by Orfila in 1814.

Lead is a slow-acting, subtle, but powerful poison. The early symptoms are often mild and, unless detected and treated, may progress to a chronic and severe illness.

Absorption.—Lead enters the body either through the lungs, by ingestion, or possibly through the broken skin, although this last-mentioned route is of little significance industrially. Any acute illness attributed to lead deserves a thorough investigation as some other substance may also be the cause of the illness.

Except for the exceedingly rare cases, it is the inhalation of lead fumes or dust which cause lead intoxication.

Storage, Distribution, and Excretion.—Following absorption from the intestinal tract, the metal passes to the portal circulation. A portion of this lead never reaches the systemic circulation for it is excreted into the bile and lost in the feces. Lead enters the body through the lungs and gains direct access to the systemic circulation. When lead once reaches the circulation, it is rapidly taken up by the tissues. The highest concentrations are found in the liver and kidneys. The element soon migrates from the soft tissue to the bone, where it is deposited in the trabeculae as the soluble tertiary phosphate salt. The metal may remain for a long period of time fixed in bone where it is probably harmless.

Lead is excreted primarily by way of the intestinal tract and kidneys. During exposure, much of the lead in the feces represents that which has never been absorbed. If a person exposed to lead is removed to lead-free environment, the amount of lead in the feces rapidly diminishes until it represents that portion of lead which is being eliminated through the intestine.

During exposure the lead content of the feces is roughly proportional to the intensity of the exposure and serves as an approximate index of its severity. On the other hand, the amount of lead in the urine gives some indication of the amount of lead which is free in the circulation. Urinary excretion, however, lags behind and does not increase directly with ingestion. The balance which exists between absorption, storage, and excretion is the main factor which determines the toxicity of lead.

Causes of Lead Poisoning.—Lead poisoning is nearly always chronic in form because the absorption of the salts of lead usually proceeds too slowly to cause acute symptoms.

Chronic industrial poisoning may occur in lead mining, smelting, and refining. Printers, painters, and pottery glazers are exposed to lead, and poisoning may occur. The manufacture of lead-containing products such as lead wire, sheet lead, bullets, storage batteries, etc., is a potential source of poisoning. Actually the industries in which lead is produced are too numerous to mention, and the majority are

too well known to make this necessary. It may be well to mention a point which is not generally known. For instance, the danger of contamination of air from molten lead starts at a much lower point than the temperature at which lead vaporizes. This is the greatest source of toxicity in printers, as fumes may come from remelting kettles and from monotype and sterotype machines.

Acute Lead Poisoning.—This condition is extremely rare. The only common soluble salt is the acetate (sugar of lead) and this is toxic only in large doses.

The usual **symptoms** include sweetish metallic astringent taste, a sense of constriction of the throat, vomiting, and constipation. The feces are usually black, and the urine is suppressed. Headache, drowsiness, cramps, and occasionally paralysis of the limbs may be observed. The patients usually recover but may exhibit symptoms of chronic poisoning.

Treatment consists of washing the stomach with a substance of magnesium or sodium sulfate, followed by water washing to remove the lead sulfate formed. Wash out bowel at regular intervals to remove excreted lead. Administer milk in large quantities, and control colic by means of atropine or morphine.

Post-mortem appearances are those of acute gastroenteritis.

Chronic Lead Poisoning.—Chronic lead poisoning is extremely important in connection with industry and factory practice, but has little criminal significance, the only cases arising in connection with attempted abortion.

Symptoms: The early signs of lead poisoning include an ashen appearance of the skin, anemia, and the appearance of a blue line along the gums. The blue line is on the gums (not on the teeth) only near dirty or carious teeth. The blood shows stippling of the red cells with basophil granules, and there may be hematoporphyrin as well as lead in the urine, and lead in the stools. If lead is not present in the urine, its excretion may be stimulated, for diagnostic purposes, by the administration of potassium iodide or parathormone.

Severe colic may be associated with the above symptoms. The patient may have a loss of appetite, show a general weakness, have a metallic taste and foul breath.

More advanced symptoms include pains in the joints; paralysis, especially of the extremities of the hands, causing wrist drop; severe frontal headache; and muscle atrophy, especially of the legs. Drowsiness, irritability, arteriosclerosis, optic neuritis, and chronic nephritis may occur.

Diagnosis: The diagnosis of lead poisoning, after years of study, is still a subject of controversy. The physician must prove: first, exposure to lead; second, absorption; third, intoxication or injury. Absorption of lead is shown by its presence in the blood and in the feces and by its effect on the blood cells. For the diagnosis of lead poisoning there must be a picture of clinical intoxication based on subjective and objective symptoms. These have already been mentioned.

Treatment of Chronic Lead Poisoning: Treatment consists essentially in preventing further absorption, keeping up the general condition of the patient, and allowing normal excretion. Excretion takes place by way of the bowel and kidneys, and is not greatly aided by the use of drugs, though potassium iodide used with care may be of some value.

Some attempt should be made to get rid of the stored lead by maintaining a negative calcium balance and altering the carbon dioxide combining power of the blood. A diet poor in calcium is given, and ammonium chloride is administered in doses of 1 Gm. in water about every two hours. Parathormone has been suggested since it produces a nega-

tive calcium balance by withdrawing calcium from the bones. Lead, like calcium, is deposited in the bone and its deposition and mobilization can be controlled. The object of treatment is to rid the body of lead at a moderate rate so that symptoms of toxicity do not appear. If severe symptoms do arise, the mobilized lead is redeposited by feeding a diet high in calcium and vitamin D.

The following treatment of lead intoxication has been adopted at the Golden State Hospital in Los Angeles. It is a simple and workable regime:

1. All patients with proved plumbism are withdrawn immediately from their occupational exposure. Even if the clinical and laboratory findings indicate a questionable or borderline case, the worker is transferred to a type of work involving no exposure to lead.
2. In those cases with mild intestinal colic, calcium is given by mouth, good intestinal elimination is encouraged, and the patient is advised to continue to work.
3. In cases of severe intestinal colic, the patient is hospitalized and intravenous calcium therapy is instituted. This is continued until the more violent colic has subsided, at which time calcium by mouth is given. All calcium therapy is stopped upon the cessation of intestinal discomfort.
4. To the general hospital diet, 20 minims of viosterol is added.
5. For the anemia, which invariably is present in the severe cases, ferrous sulfate is prescribed.

Under this regime it was not necessary to use morphine, atropine sulfate, nitroglycerin, or amyl nitrite, which are commonly used in other methods of treatment.

BAL has been reported as probably useful in the diagnosis and treatment of lead poisoning (Telfer, J. G.: J. A. M. A. 135: 835, 1947). The urinary lead is distinctly increased by its administration. The amount of lead eliminated by a single dose (5 mg.) is too small to have therapeutic significance and repeated injections are liable to induce toxicity (Ryder et al., 1947).

Metal Fume Fever

Metal fume fever is found in workmen engaged in smelting brass or zinc or electric arc welding. It is not a true metal poisoning but is the result of damage to the epithelial cells of the respiratory tract. Absorption of these altered proteins of the cells causes a reaction such as occurs in typhoid fever. Cases are becoming numerous.

Symptoms appear two to twelve hours after exposure. Chilling of the body is often the exciting cause, and cases are more numerous in the winter. The actual chill is preceded by a feeling of dryness in the throat, with cough; oppression in the chest; occasionally nausea, and rarely vomiting. The chill is followed by sweating and general weakness, which disappears by morning and the patient returns to work.

The hazard is the zinc product mostly, because galvanized steel is 95 per cent or more zinc and only 1 per cent lead. However, the same condition may occur in manganese, copper, brass, and bronze welders. Fortunately iron and aluminum oxides do not cause these reactions. The new types of alloys being developed contain manganese, selenium, arsenic and cadmium, and all are toxic. The necessity of welding stainless steel and aluminum has caused the inhalation of calcium fluoride which is extremely caustic to the respiratory tract.

Treatment.—Preventive treatment is important. The toxic fumes should be controlled at their source. Masks and respirators and, better still, proper ventilation is of paramount importance.

No specific treatment is indicated. Relief may be afforded by the administration of acetylsalicylic acid (0.6 Gm.) and codeine phosphate (30 mg.) every four to six hours. The forcing of fluids, the use of hot drinks, and rest are of value.

Cadmium

Cadmium, of late, has become of increasing importance in industry as an ingredient of alloys, and in electroplating. Poisoning from cadmium is a rare finding, but apparently many cases go unrecognized. Poisoning usually occurs from accidental overheating of cadmium. Poisoning has been reported also from eating acid-containing foods left standing in cadmium-plated cooking utensils or "ice-cube" trays.

Symptoms.—The action of cadmium fumes and dust is primarily on the lungs. The symptoms resemble those of nitrous fume poisoning —weakness, dyspnea, pain in the chest, coughing, and profuse sweating.

Treatment: Prophylactic.—Workmen should wear respirators at all times when near cadmium fumes.

A patient overcome with fumes should be placed immediately within an oxygen tent. Patients less seriously affected may obtain relief from the following drugs: acetylsalicylic acid 0.6 Gm. (10 gr.) every four to six hours; capsules containing acetylsalicylic acid 0.3 Gm. (5 gr.), phenacetin 0.15 Gm. (2½ gr.), and citrated caffeine 30 mg. (½ gr.), at three-hour intervals. A combination of ephedrine sulfate 8 mg. (⅛ gr.), and amytal 24 mg. (⅜ gr.), at four-hour intervals may afford some relief.

Irrigation of the throat with a sodium chloride and sodium bicarbonate solution (one teaspoonful of each in a pint of warm water) may be undertaken. If irrigations are difficult, use the above solution as a *gargle*.

Selenium and Tellurium

Selenium is used chiefly in glass and pottery manufacture, and also as a catalyst in making photo-electric cells. Tellurium, which is used to strengthen steel, gained importance during the war.

Symptoms.—Selenium and tellurium both have much the same physiological action, but differ in that tellurium inhibits sweat, selenium does not. Both cause a garlic odor to the breath before symptoms of poisoning occur. Other common symptoms include dryness of the mouth, metallic taste, scaly itchy skin, anorexia, nausea and vomiting. Drowsiness and apathy are characteristic symptoms.

Treatment.—No specific treatment is available. Remove patient from exposure. The use of diuretics to secure elimination may be useful, e.g., ammonium chloride, 1 Gm. (15 gr.), three times daily. Magnesium sulfate, 15 to 30 Gm. (½ to 1 ounce) is also useful.

Treat upper respiratory symptoms. Intravenous 50 per cent dextrose, 50 to 100 cc., may aid edema of the lungs. Inhalation of oxygen by intranasal tube, or by use of a tent, may be needed. A diet high in carbohydrates and rich in vitamin B complex has been suggested.

Cyanides and Hydrocyanic Acid

Sodium and potassium cyanide are used on a large scale in industry in electroplating, cleaning and coating silver, hardening steel, tanning, and in calcium cyanide as a fertilizer. Hydrogen cyanide is used for the fumigation of ships and homes and for the destruction of plant

parasites. Acrylonitrile (CH_2CHCN COOH), is a new industrial cyanide used in the production of synthetic rubber. The latter resembles hydrocyanic acid very closely in toxic action. Acute poisoning from cyanides is rare and chronic poisoning is even more so.

Suicide and homicide continue to be the chief factors in fatal cyanide poisoning. Sodium cyanide, potassium cyanide, hydrogen cyanide (hydrocyanic acid), and calcium cyanamide, are the chief compounds of interest.

Symptoms.—The cyanide salts produce corrosive action in the upper respiratory tract and especially in the stomach; after absorption the cyanide radical inactivates certain oxidative enzymes of the tissues which prevent tissue utilization of oxygen carried by the blood. In early cyanide poisoning cyanide reflexly stimulates respiration by action on the sensory nerve endings in the carotid body.

The symptoms are dizziness, vertigo, palpitation, dyspnea, cyanosis, and unconsciousness. Circulatory function may be strong or weak; the pupils are dilated. Vomiting frequently occurs before loss of consciousness. Such vomitus often has the characteristic peach-kernel odor.

The *fatal dose* of sodium or potassium cyanide is about 0.25 Gm. (4 grains). Hydrogen cyanide is about twice as toxic as its salts. Cyanide salts are rapidly *absorbed* from the alimentary tract, cyanogen (C_2N_2) and hydrocyanic acid from the respiratory tract. Cyanide is *oxidized* in the body to cyanate and sulfocyanate and is then *excreted* in the urine. *Death* is caused by asphyxiation. The *autopsy* findings are those of asphyxia. *Diagnosis* may be aided by the characteristic peach-kernel odor of the vomitus. Air hunger out of proportion to the degree of cyanosis or in the presence of bright venous blood is suggestive.

Treatment.—

1. Amyl nitrite inhalation.
2. Sodium nitrite, intravenously, 0.3 Gm. in 10 cc. of sterile distilled water.
3. Sodium thiosulfate, intravenously, 12.5 Gm. in 50 cc. of sterile distilled water.

Rationale of Treatment.—The treatment depends upon the prevention of muscular rigidity and convulsions by the action of amyl nitrite. Sodium nitrite converts hemoglobin into methemoglobin which more readily unites with the hydrogen cyanide, forming cyanmethemoglobin. The sodium thiosulfate synergizes the action of sodium nitrite.

Chlorinated Hydrocarbons

These solvents are noninflammable, have excellent solvent action, and are useful as textile cleansers, solvents for rubber and gums, degreasers of metal, and as cellulose lacquer thinners. They are used also in the production of high-grade lubricating oils, manufacture of vegetable oils, the purification of explosives, and for refrigeration. Important chlor compounds include the following:

CARBON TETRACHLORIDE (CCl_4). This compound is used as a chemical fire extinguisher, for dry cleaning, and medically as an anthelmintic.

Symptoms.—Carbon tetrachloride is a narcotic with an action much like chloroform though not as strong. The aftereffects seem to be more serious than those of delayed chloroform poisoning and they occur more often. The symptoms observed from industrial poisoning are those of acute narcotic intoxication, followed by signs of liver

and kidney damage. The history is usually one of nausea, vomiting, abdominal pains, diarrhea, headache, dizziness, dark-colored urine, jaundice, and increasing oliguria with urine containing albumin and casts. Complete anuria may occur.

Chronic poisoning resulting from prolonged exposure to small amounts of carbon tetrachloride may sometimes be encountered. It rarely occurs, however, and the symptoms are less characteristic than the acute type.

Treatment.—Poisoning may be prevented by proper ventilation. The possibility of skin contact should be eliminated. The diet of workers should be high in calcium, and alcoholic beverages should be avoided.

When poisoning does occur, treatment is directed at repair of liver and renal damage and restoration of blood chemistry. Patients are given a high calcium intake to prevent liver and renal damage. Twelve grains of calcium gluconate may be given orally each day and intravenous injections of 10 cc. of 10 per cent solution of calcium gluconate three times daily. A diet high in carbohydrates and low in fat and proteins is indicated. The intravenous administration of 2,000 to 3,000 cc. of 10 per cent dextrose in physiological saline, daily, is indicated. Other medication may be necessary, including diuretics, cathartics, and blood transfusions.

TRICHLOROETHYLENE ($CHCl.CCl_3$). Next in importance and used often for the same purpose as carbon tetrachloride is trichloroethylene.

Symptoms.—Trichloroethylene is less toxic than carbon tetrachloride but possesses an acute narcotic action like chloroform. Acute narcosis is a characteristic symptom. Psychic disturbances are well known; hysteria is common; trichloroethylene addiction is well established; personality changes take place. Minor effects include headache, dizziness, anorexia, nausea and vomiting.

Treatment.—Proper ventilation is an important prophylactic measure. Exposed areas on workers may be protected by a suitable ointment containing equal parts of petrolatum and rose water ointment.

When acute poisoning occurs, artificial respiration may be indicated. Inhalations of oxygen and 5 to 7 per cent carbon dioxide are most valuable. In shock, transfusions of citrated blood and the intravenous infusion of 1,000 cc. of 10 per cent dextrose in normal saline solution are administered.

If the patient has been exposed to phosgene resulting from decomposition of trichloroethylene by gas flames, the picture may be one of pulmonary edema, dyspnea, and cyanosis. Respiratory and circulatory stimulants are indicated and probably venesection of 500 cc. in pulmonary edema.

ETHYLENE DICHLORIDE ($ClCH_2.CH_2Cl$).—This compound is an excellent solvent but a dangerous poison. It is used in the separation of wax from petroleum, in dry cleaning, in oil purefaction, in the production of photographic films, and in the paint industry.

Symptoms.—The narcotic action is about equal to that of carbon tetrachloride but there are less serious aftereffects. Symptoms commonly present, after long exposure, include anorexia, nausea, vomiting, epigastric distress, drowsiness, tremors, and nystagmus. Severe dermatitis of the hands, leukocytosis, and liver disturbances have been reported.

Treatment.—Remove patient from fumes and treat with calcium and a high carbohydrate diet. As in the treatment of the other solvents, intravenous infusions of 5 to 10 per cent dextrose in physiological solution of saline are indicated.

CHLORINATED NAPHTHALENES.—These are excellent insulating waxes for electrical insulation. In this country, Halowax has been the source of a skin lesion called "cable rash."

When higher members of this group, penta- and hexa, came into use, cases of fatal jaundice, and acute yellow atrophy of the liver were reported.

Treatment.—Proper ventilation is indicated to prevent toxic manifestations. No specific treatment is available. The skin lesions may be treated by quartz light and x-ray therapy. The pustules may be opened and treated locally with sulfathiazole ointment. The liver damage may respond to a high carbohydrate diet, with adequate fluid intake and intravenous infusions of 5 to 10 per cent glucose in saline.

Coal Tar Benzene or Benzol

Benzene (C_6H_6) is one of the most dangerous of industrial solvents. The basic pathology underlying benzene poisoning is that it acts chiefly on blood-forming tissues, the marrow of the long bones, and the lymphatic structures, producing anemia and granulocytopenia with loss of ability of the blood to clot. Chronic poisoning is of far more importance in industry than acute.

Symptoms.—The clinical picture of chronic benzol poisoning includes progressive weakness, dizziness, headache, and vomiting. Next, purpuric spots appear on the skin. Bleeding from the gums, throat, and nose is common. An examination of the blood during the bleeding stage shows marked changes, an anemia of the nonregenerative type, granulocytopenia, and prolonged bleeding and clotting time. Diagnosis may be easy if benzene exposure has been reported.

The newer knowledge of benzene poisoning may be summarized as follows:*

1. The diagnosis of benzene poisoning, mild or severe, must be made on the whole blood picture, and the earliest and most frequent deviation from the normal consists in a fall in the red cell count and an increase in the mean corpuscular volume of the red cells. A fall in platelet count and a reduction of hemoglobin follow in frequency, but a fall in the white cell count is less characteristic of early poisoning than any of the above. Anemia and macrocytosis are the changes to be looked for.

2. Increase of urobilinogen and deviation from the normal urine sulfate partitions were not found to be of value in diagnosis.

3. Bleeding time and coagulation time were of no aid, being prolonged only in severe cases.

4. Clinical symptoms, weakness, fatigue, epistaxis, dryness of the throat, anorexia, nausea, dizziness, insomnia, were of dubious value, because, although they were present in workers exposed to benzene more than in controls, they were absent in some cases of serious poisoning.

5. Purpura, particularly bleeding from the mucous membranes, was relatively rare, being absent in some severe cases.

6. In severe poisoning the blood may show changes like those in pernicious anemia.

7. An aplastic marrow is not typical of benzene poisoning; hyperplasia may be found even more often.

*Benzene (Benzol) Poisoning Symposium, J. Indust. Hyg. & Toxicol. 21: 321, 1939.

8. A study of the hyperplastic cases reveals what may be called a neoplastic tendency, rapid growth as shown by mitotic figures, the development of cells having no counterpart in normal tissues but being common to a variety of malignant tumors.

Carbon Disulfide

Carbon disulfide (CS_2) is a heavy volatile liquid of characteristic odor and insoluble in water. It is highly inflammable.

Sources of Poisoning.—Carbon disulfide is an industrial poison. It is widely used because of its properties as an industrial solvent for sulfur, rubber, viscose, and other industrial chemicals. The chief danger to the worker is from inhalation of the vapor.

Symptoms.—The symptoms of carbon disulfide poisoning are due primarily to its toxic action on the blood, converting hemoglobin to methemoglobin; secondarily, because of its lipoid solubility it quickly attacks the nervous system.

Liquid carbon disulfide is highly irritating to the skin and mucous membranes. It produces a burning sensation; blistering is common and injury to nerve fibers may result from exposure. *Acute poisoning* is commonly associated with headache, nausea and vomiting, hyperemia of the skin, pain in the limbs, excitement or depression, and finally respiratory paralysis. *Chronic poisoning* is characterized by headache, fatigue, anorexia, gastrointestinal symptoms, anemia, insomnia, visual disturbances, and paresthesias. Psychic changes are frequent. Neuritis, partial blindness and symptoms associated with degenerative changes in all parts of the central nervous system may occur.

A teaspoonful of carbon disulfide may produce *toxic* symptoms. The inhalation of concentrations of 10 parts per million of air may produce symptoms, and 50 parts per million of air may cause fatal poisoning. The liquid is *absorbed* from the gastrointestinal tract and the skin; the vapor is absorbed by the lungs. It is *excreted* unchanged by the lungs and kidneys. *Death* is caused by central nervous system depression with respiratory failure. Chronic poisoning may lead to death from inanition, or hepatic insufficiency. The *autopsy* findings show areas of degeneration throughout the nervous system. Degenerative changes are also found in the heart and liver. During life *diagnosis* is made by the history or by determination of the concentration of carbon disulfide in blood or expired air.

Treatment.—*Acute Poisoning* (rare):

1. Gastric lavage—warm water.
2. Artificial respiration—CO_2, 5 per cent, and O_2, 95 per cent.
3. Blood transfusion.

Chronic Poisoning: Adequate ventilation is the most important factor as a prophylactic. Monthly medical examination for those exposed is indicated.

No specific treatment for chronic carbon disulfide poisoning is known. A diet high in vitamin B complex, supplemented by 50 to 60 mg. of thiamine chloride, parenterally, daily, and 200 mg. of nicotinic acid daily, 1 mg. of riboflavin three times daily, and 20 mg. of vitamin B_6, parenterally, twice daily. A program of mental hygiene is recommended. An ophthalmologist should be consulted on problems related to the eyes.

Carbon Monoxide

Carbon monoxide (CO), a colorless, odorless, and tasteless gas, is the most prevalent and most insidious of the toxic gases encountered in modern civilization. Its victims are found in domestic life, in transportation, and in industry.

Sources.—Automobile exhaust gas contains about 7 per cent of carbon monoxide. Mine explosion gases, industrial blast furnace gas, and fuel gases contain 8 to 30 per cent carbon monoxide. Furnace gases in homes contain about 1 per cent carbon monoxide. Lack of proper maintenance, improper construction, and defective ventilation are frequent causes of carbon monoxide poisonings. Automobile exhaust gas from running motors in closed garages or in repair shops results in many carbon monoxide poisonings each year. While natural gas contain no carbon monoxide, manufactured gas, so widely used as fuel, contains about 20 per cent.

Physiological Effects of Carbon Monoxide.—Carbon monoxide has an affinity for combination with hemoglobin of the blood approximately 300 times that of oxygen. In an atmosphere containing this gas the oxyhemoglobin of the blood is converted to carbon monoxide hemoglobin, thus excluding the necessary supply of oxygen to the body tissues and ultimately resulting in asphyxiation if the concentration of carbon monoxide in the air breathed and the duration of exposure are sufficient. The reaction between carbon monoxide, oxygen, and hemoglobin is a reversible one, following the well-known "mass law" of chemistry. In the presence of fresh air or oxygen the reaction proceeds in the reverse manner: oxyhemoglobin is formed and carbon monoxide is eliminated. Carbon monoxide is classified as a chemical asphyxiant, not as a direct tissue poison.

The erythrocytes are not injured by the combination of carbon monoxide with hemoglobin. They are deprived of their vital oxygen-carrying function. After removal of carbon monoxide from the blood, however, their normal function is restored. The sequelae of carbon monoxide poisoning are attributed to the extent and duration of the anoxemia caused by the formation of carbon monoxide hemoglobin. It is for this reason that it is important to eliminate the carbon monoxide from the blood as soon as possible in order to prevent permanent tissue damage.

Rate of Absorption.—The rate at which carbon monoxide hemoglobin is formed in the blood is dependent upon the concentration of the gas in the air breathed, the duration of exposure, the activity of the in-

TABLE V

PREDOMINATING SYMPTOMS OF CARBON MONOXIDE POISONING

	PER CENT BLOOD SATURATION
No symptoms	0-10
Tightness across forehead; slight headache, dilation of cutaneous vessels	10-20
Headache; throbbing in temples	20-30
Severe headache, weakness, dizziness, dimness of vision, nausea and vomiting, collapse	30-40
Same as previous; more tendency toward collapse and syncope; increased respiration and pulse	40-50
Syncope, increased respiration and pulse; coma with convulsions; Cheyne-Stokes respiration	50-60
Coma with intermittent convulsions; depressed heart action and respiration; possibly death	60-70
Weak pulse and slowed respiration, respiratory failure and death	70-80

dividual, and to a less extent upon age, high temperature, humidity, and individual susceptibility.

Sayers and Yant found the symptoms as recorded in Table V as the percentage of carbon monoxide increased.

On the other hand, Gettler (Am. J. Clin. Path. 13: 169, 1943) found that 25 per cent of persons died from carbon monoxide saturation of less than 60 per cent; 28 per cent died from saturation between 60 and 70 per cent, and 48.5 per cent died from saturation between 70 and 88 per cent.

Elimination of Carbon Monoxide.—Removal to fresh air is of first importance in the treatment of carbon monoxide poisoning in order that replacement of oxygen for the combined carbon monoxide in the blood may be accelerated. Under such conditions about 50 per cent of the carbon monoxide is eliminated during the first hour. However, complete elimination requires several hours. Elimination of carbon monoxide may be speeded up by administration of pure oxygen or a mixture of oxygen plus carbon dioxide (93:7). The carbon dioxide stimulates the respiratory activity by increasing the frequency and depth of respiration.

Concentrations of 400 to 500 parts of carbon monoxide per million parts of air have no appreciable effect after one hour of breathing, whereas four times this amount in one hour is dangerous and 4,000 parts per million are fatal in less than one hour. The exhaust gas of an automobile contains 7 per cent carbon monoxide (70,000 parts per million parts air) and is sufficient to render the air in an average garage deadly in five minutes if the engine is allowed to run and the garage doors are closed.

Acute Poisoning.—In acute carbon monoxide poisoning there may be an absence of subjective symptoms, the victim being either unconscious or in a state of much confusion. This acute form of poisoning is manifested by progressive paralysis of the central nervous system, and results in an increase in pulse and respiratory rates; fall in blood pressure; loss of reflexes; loss of muscular control, especially the sphincters, and finally coma with intermittent convulsions; Cheyne-Stokes respiration; slowing of pulse; slow and shallow respiration; cessation of respiration; death. If the patient recovers, permanent damage may have been done to the brain, due not to absorbed carbon monoxide but to an insufficient supply of oxygen in the blood. It is the intensity and duration of the period of asphyxiation which are related to such late symptoms and sequelae as are listed by Mayers.

1. Headache
2. General weakness, especially of the muscles.
3. Pain in the limbs, with or without numbness or tingling.
4. Tremor.
5. Palpitation of heart, with shortness of breath.
6. Attacks of intense pain or pressure over heart region, resembling angina pectoris.
7. Anemia.
8. Extreme dryness of throat.
9. Various mental or nervous symptoms.

Chronic Poisoning.—There may be no such thing as chronic carbon monoxide poisoning *per se*. If you are going to have poisoning, so called, from repeated acute exposures, then this condition should be known clinically as encephalitis or postasphyxial myelitis. Nevertheless, whether there is chronic poisoning or not there is ample evidence that long periods of exposure to low concentrations of carbon monoxide are responsible for distressing symptoms which interfere with the health of the individual.

The clinical picture is varied. In most cases the complaints are frequent headaches, nausea, vomiting, general muscular weakness with increased fatigue. Severe manifestations have been reported, such as loss of vision, narrowing of visual field, joint pains, and muscle spasms.

The diagnosis of chronic exposure to carbon monoxide may be established by *air analyses* and by examination of the patient's blood for carbon monoxide content. The blood sample, of course, must be taken during or immediately after the exposure because of the instability of carbon monoxide hemoglobin on removal of the patient to fresh air.

Diagnosis.—The diagnosis of nonfatal carbon monoxide poisoning is not easy in the absence of a history of exposure to gas. With large concentrations of carboxyhemoglobin the skin may show a pinkish flush, but this is not always apparent in the living patient. Carbon monoxide should be suspected in obscure cases of coma attended by marked spasticity of the extremities and by the presence of hyperactive and abnormal deep reflexes, clonus, and signs suggesting bilateral involvement of the pyramidal tracts.

To establish the diagnosis in nonfatal poisoning remove, as soon as possible, a sample of blood (15 cc.) for qualitative and quantitative chemical examination for the presence of carboxyhemoglobin. *Qualitative test:* Dilute a few drops of blood, then add a few drops of 10 per cent sodium hydroxide. A light pink solution will result and persist after the addition of the alkali. Normal blood will turn a greenish brown on the addition of the alkali. Qualitative tests as well as spectroscopic tests for carboxyhemoglobin will give positive tests only if the concentration of carboxyhemoglobin in the blood is more than 10 per cent.

In fresh air, about half of the carbon monoxide in the system will be eliminated during the first hour of survival; after twenty-four hours, all the carbon monoxide will have disappeared. Thus for medicolegal purposes secure blood sample immediately after exposure.

In acute carbon monoxide poisoning, many persons may survive for twenty-four hours or more. They may regain consciousness only to lose it again and die. A hypostatic bronchopneumonia may set in. *At autopsy:* patients surviving for more than twenty-four hours after poisoning may show a bilateral symmetrical softening or necrosis of the globus pallidus.

Carbon monoxide is not a cumulative poison in the sense of being stored in the body. The critical examination of persons who have had repeated small exposures reveals the production of no known characteristic lesions. The condition of the nervous system and the cardiac lesions attributed to such exposure have been exaggerated. From 30 to 75 per cent of the hemoglobin is saturated with carbon monoxide in carbon monoxide deaths. Lower percentages are found in those who die of short exposures. *Quantitative determination* of the carbon monoxide content of the blood should be carried out with the Van Slyke manometric apparatus.

Treatment.—*Get patient into the fresh air immediately.* If breathing has stopped or is irregular apply artificial respiration. Oxygen-carbon dioxide inhalation may be indicated. Five per cent carbon dioxide in oxygen is preferable but pure oxygen may be used if this is not available. Carbon dioxide stimulates respiration and promotes the replacement of carboxyhemoglobin with oxyhemoglobin. In those patients where breathing is difficult or has stopped artificial respiration by the Schaefer method should be given until normal breathing is restored. The application of external heat and a long period of rest are usually indicated for complete recuperation. Drugs are of little value in car-

bon monoxide poisoning. Dr. Drinker says—"It is a fact that practically every possible or impossible drug has been used in carbon monoxide poisoning, and it is doubtful if any of them influence the result."

Note: Methylene blue, once thought to be an antidote, is of no value and is contraindicated.

Rationale of Treatment.—The intoxication is due to the formation of carboxyhemoglobin by union of carbon monoxide with oxyhemoglobin. High oxygen tension tends to convert carboxyhemoglobin to oxyhemoglobin and thus to combat the anoxemia and anoxia. Carbon dioxide stimulates the respiratory center.

Radioactive Substances

The use of radioactive substances in industry is very recent. Industrial exposure to these substances occur in mining radioactive ores, testing the ores, making up radon seeds, and applying luminous paint to timepieces and apparatus.

Radium is formed by the natural radioactive decay of its parent, uranium, which occurs in mineral deposits. Radium disintegrates and emits alpha rays. The alpha ray can travel about 50 microns in living tissue, and can do lethal damage to most of the cells through which it passes.

Symptoms.—Industrial exposure to radioactive substances may produce pulmonary carcinoma, necrosis of bone, malignant growth of bones, and various primary blood diseases.

Treatment.—Prevention of radium poisoning is directed against inhalation of dust. Individual glass masks are commonly employed. Suction ventilation should be used to keep the air relatively clean. Rigid personal hygiene such as washing of the hands, etc., is important. A complete blood count should be made once each month. The worker should undergo radon measurements (Evans). Prevention of radium absorption may be aided by an adequate calcium intake.

In chronic poisoning, treatment is directed toward aiding radium excretion. Parathyroid extract plus large doses of ammonium chloride have been recommended. Treat any existing anemia.

Petroleum Distillates

Petroleum and its distillates, gasoline, benzine, naphtha, petroleum ether, and kerosene are mixtures of hydrocarbons, paraffins, olefins, naphthenes, and aromatics. These substances are narcotic poisons, but much larger doses are required to produce poisoning than with other industrial solvents.

Symptoms.—In acute poisoning the symptoms are those of a narcotic drug—fullness of head, blurred vision, headache, dizziness, ataxia, and nausea. Massive doses result in sudden collapse, coma, and sometimes death. Autopsy findings are not characteristic. Hemorrhages in the lungs are often present.

Chronic symptoms resulting from benzine poisoning include restlessness, vomiting, dyspnea, and tonic muscle spasms. Pains in the limbs, coldness and numbness in the hands, loss of strength and memory have been reported.

Treatment.—In acute poisoning the treatment is aimed at preventing respiratory and circulatory collapse. In severe cases pulmonary edema may be best handled by positive pressure therapy. Oxygen by catheter or tent is indicated if positive pressure therapy is impossible.

Keep patient warm. If circulatory failure is present, administer caffeine and sodium benzoate, 0.5 Gm. (7½ grains), or metrazol, 0.1

to 0.3 Gm. (1½ to 4½ grains), intramuscularly. Pulmonary complications should be treated if they arise. Treat nervousness and restlessness with such drugs as chloral hydrate, 0.6 to 2.0 Gm. (10 to 30 grains), or sodium bromide, 0.6 to 2.0 Gm. (10 to 30 grains). Venesection may be indicated to rid the body of methemoglobin.

Petroleum distillate fumes produce conjunctivitis which may be treated by dropping 1:1,000 epinephrine solution into the eyes three to four times daily. Boric acid ointment and cold compresses may be of value.

Chronic cases should be removed from exposure. A high caloric vitamin diet is indicated. Treat any anemia present with ferrous sulfate preparations.

Synthetic Rubber

New toxic substances have appeared with the manufacture of synthetic rubber, such as acrylonitrile, butadiene, and monomeric styrene. The first has been referred to under cyanides.

Butadiene is a gas with a mildly narcotic action. The vapors cause irritation of eyes and respiratory passages. Styrene produces eye and nose irritation. Its fumes produce mild narcotic symptoms.

Treatment.—Butadiene often produces skin burns. It is interesting to know that a patient frequently is unaware that his skin has been burned until several hours after contact. Anyone exposed to this substance should take a shower bath and change his clothes. Calamine lotion may be applied over the body.

Toxicology of Other Drugs

The reader is referred to the index for the toxicology of the various other drugs.

War Gases

A number of more or less poisonous gases are used in warfare. Every medical man should be familiar with these substances in regard to recognition and immediate treatment.

It is impossible to give a detailed account of these gases in this text. In general the gases so far used may be divided as follows:

1. Lacrimators (Tear Gases)
   - Chloracetophenone ($C_6H_5.CO.CH_2Cl$) (C.A.P.)
   - Bromobenzylcyanide ($C_6H_5.CHBr.CN$) (B.B.C.)
2. Sternutators (Nose Irritants)
   - Diphenylchlorarsine $(C_6H_5)_2.AsCl$
   - Diphenyl-cyanarsine $(C_6H_5)_2.AsCN$
3. Pulmonary Irritants
   - Chlorine (Cl_2)
   - Phosgene ($COCl_2$)
   - Diphosgene ($Cl.COOCCl_3$)
   - Chloropicrin (CCl_3NO_2)
4. Vesicants (Blister Gases)
   - Mustard Gas $(CH_2Cl.CH_2)_2S$
   - Lewisite ($Cl.CH:CH.AsCl_2$)

The tear and nose irritant gases are used primarily to cause temporary distress, and rarely cause casualties. High concentrations may, however, cause pulmonary irritation. The symptoms are obvious, and the treatment consists of washing the ears or the nose with 2 per cent sodium bicarbonate solution.

PHOSGENE ($COCL_2$) may be taken as a type of the pulmonary irritants. It is colorless but is recognized by its musty hay odor.

Symptoms.—There is coughing and difficulty of respiration with a feeling of burning and constriction in the chest. Longer exposure causes pulmonary edema and even death from asphyxia. Symptoms develop several hours after exposure. The majority of deaths occur during the first twenty-four hours.

Treatment.—Place patient at absolute rest. Warmth is essential. Oxygen should be administered and irritating cough should be treated with codeine. Acidosis may be treated by the intravenous administration of 500 cc. (1 pint) of 5 per cent sodium bicarbonate. For collapse, give caffeine and sodium benzoate, 0.5 Gm. (7½ grains), subcutaneously.

MUSTARD GAS or dichlorethyl sulfide is a liquid which vaporizes slowly at ordinary temperatures, giving off mustard gas. It has a mustard or garliclike odor. It is very penetrating.

Symptoms.—On exposure, there is little effect for a few hours, after which the eyes and nasal passages show marked irritation. The throat becomes dry and burning, and vomiting and gastric pain soon follow. During the first twenty-four hours the eyelids become swollen and blisters form on the skin. The whole respiratory tract may become inflamed, resulting in the production of areas of ulceration and necrosis. Bronchopneumonia may result and cause death.

LEWISITE is quite similar to mustard gas but the action is more rapid. It may be complicated by symptoms of acute arsenical poisoning.

Treatment.—Early treatment consists in removal of the patient to fresh air and immediate treatment of skin and eyes.

SKIN TREATMENT.—*Mustard gas:* Dab and cleanse skin with sponges dampened with gasoline (nonleaded), kerosene, alcohol, sodium hypochlorite, or chloramine-T. Scrub skin with soap and water. *Lewisite:* Remove agent with peroxide or 10 per cent sodium hydroxide in glycerin.

EYE TREATMENT.—Irrigate eyes immediately with a 2 per cent solution of sodium bicarbonate. Petrolatum may be applied to the edges of the eyelids to prevent sticking. A 2 per cent solution of butyn may be instilled in the eyes to relieve pain. *Do not use cocaine or antiseptics in the eyes.*

Eyes contaminated with the liquid Lewisite should receive repeated instillations of 0.5 per cent hydrogen peroxide or 2 per cent sodium bicarbonate. Expert attention is indicated in these cases.

Late treatment of lesions produced by vesicants is as follows: *Mustard:* Débride and apply sulfadiazine locally as a powder. Boric acid or Burrow's solution (diluted) as wet dressings may be useful. Finally, a triple-dye mixture or tannic acid solution may be sprayed on the lesion to produce a protective coating. *Lewisite:* Burns caused by this agent may be excised, even though the area involved is quite large (up to 12 sq. in.); they will usually heal by first intention. BAL by local application and systemic administration is indicated (see under Arsenic).

METHODS OF DETECTION AND ISOLATION OF POISONS

The methods employed in tracing the cause of poisoning and determining the nature and quantity of the poisons involved may be divided into three classes: (1) physical methods, (2) biological methods, and (3) chemical methods. ***The chemical methods are by far the most important.***

1. Physical Methods.—Various optical and colorimetric methods may be employed for detecting poisons. Colorimetric tests are

valuable in the detection of alkaloids. The refractive index may be employed in micromethods for detection of small amounts of poisons. The spectroscope is of utmost importance in detecting poisons in the blood.

2. **Biological Methods.**—These methods are of importance because of the great sensitivity of biological tests. Hatcher has been able to detect traces of strychnine much more readily by biological means than is possible by physical or chemical means.

The pharmacologist may employ even plant life to aid in his hunt for poisons. Poisons may be detected by their effects on ferments; for example, formaldehyde, phenol, mercuric chloride, etc., may be detected by their poisonous effect on yeast cells. Worms may be used for the detection of anthelmintics and other drugs. Blood corpuscles are often used for the detection of saponins, toxic albumins, and metals.

Biological tests can generally be obtained with substances less pure than are required for chemical tests. They are most valuable for detecting substances like strychnine, atropine, physostigmine, aconite, "digitalis bodies," and veratrine.

3. **Chemical Methods.**—The examination of the toxicologist consists chiefly of a chemical analysis of the organs, excretions, or tissues of the body in order to determine whether or not poisons are present.

Poisons are chemical compounds. They exhibit characteristic boiling points, solubilities, color reactions, and other chemical reactions. On the basis of the various chemical properties poisons are isolated, purified, and identified. *The chemical analysis should be performed by an experienced toxicologist.*

CHEMICAL METHODS OF TOXICOLOGICAL ANALYSIS

A general knowledge of the principles and technique of a toxicological examination is indispensable to a physician. Such information will aid him in performing certain of the simpler toxicological tests and, of still greater importance, it will aid him in interpreting analyses made by the toxicologist. This knowledge is essential to a physician when called upon to testify in court.

Preliminary Procedures.—The pathologist and toxicologist usually work as a team. The pathologist should examine the various structures and remove sections for future histological study. The material for chemical examination, after being examined by the pathologist, should be placed immediately by the pathologist in clean glass jars with tight covers. *Each jar should be properly labeled.*

PRESERVATION OF TISSUES.—When immediate analysis is to be made or analysis for volatile material is indicated, no preservative is added. Tissues for analysis should be removed before the body is embalmed. When the analysis cannot be made immediately, the tissues should be preserved chemically or by refrigeration. *Refrigeration is the method of choice.* Alcohol (95%) or formaldehyde (4%) must *not* be used if ethyl alcohol or methyl alcohol, carbon monoxide, cyanide, or phenol is suspected. In the latter case use one part of salt to three parts of tissue until the removal of the volatile substances has been accomplished.

TISSUES TO BE EXAMINED.—It is rarely necessary to examine the whole body. As a rule, the following organs are analyzed and in the following order: the stomach and contents, the intestines, the liver, spleen, kidneys, heart, lungs and brain; it may, however, be necessary to examine other organs. If the poison is known, certain tissues known to contain the poison may be selected for examination.

Blood, urine, gastrointestinal contents, liver, lungs, kidney, and spleen should be taken routinely. Any samples of vomitus or gastric washings should be saved.

The materials best adapted for chemical analysis are:

TABLE VI

MATERIAL FOR TOXICOLOGICAL ANALYSIS

POISON	BLOOD	URINE	VOMITUS	BRAIN	LIVER	KIDNEY	STOMACH	INTESTINE	FECES	BONE	HAIR
Acids			X				X	X			
Alkali							X	X			
Alcohol	X	X		X							
Benzene	X	X		X	X						
Cyanides	X		X	X	X		X				
Chlorates	X	X	X		X		X	X			
Carbon tetrachloride		X	X		X		X				
Barbitals	X	X		X	X		X				
Alkaloids		X	X	X	X		X	X			
Strychnine			X	X	X		X				
Nicotine		X	X	X			X	X			
Morphine		X	X	X	X		X				
Antimony		X	X		X	X	X	X	X	X	
Arsenic	X	X	X		X		X	X	X	X	X
Fluoride	X		X		X		X	X			
Lead	X	X	X	X	X		X		X	X	
Mercury			X	X	X	X	X	X	X		
Phosphorus			X		X	X	X	X			
Phenol		X	X				X				
Carbon monoxide	X	X									

PREPARATION OF MATERIAL TO BE EXAMINED.—After the tissues have been examined (gross appearance, color, odor), they should be weighed and finely divided by means of scissors or meat grinder. The mixture is divided into four equal parts: one part for control and preliminary tests; one part for the volatile poisons; one part for fixed organic poisons (nonalkaloidal, alkaloidal); the fourth part for metals. Poisons, from the analytical point of view, may be conveniently divided into four classes: (1) volatile poisons obtained from suspected material by steam distillation, (2) nonalkaloidal organic substances, soluble in ether in the presence of acid, (3) alkaloids, soluble in ether or chloroform in the presence of alkali, and (4) mineral poisons.

THE SCHEME OF CHEMICAL ANALYSIS

Volatile Poisons

(Steam distillation)

PROCEDURE: Weigh out 100 Gm. of tissue; place it in a distillation flask with 100 cc. of water and a crystal of tartaric acid; connect to a Liebig condenser. Fit an adapter to the condenser tube, dip into a few

cubic centimeters of water, distill over 100 to 150 c.c. of water. Distillation is best carried out by the use of steam from a second flask connected to the flask containing the material. The distillate may contain hydrocyanic acid, ethyl alcohol, etc. Next make the contents of the flask alkaline with magnesium oxide and steam distill again. In the alkaline distillate may be found ammonia, amines, aniline, volatile alkaloids, and other volatile bases.

Note: Distillation under reduced pressure with efficient cooling of the distillate minimizes destruction of nonvolatile organic poisons, especially alkaloids, and facilitates the procedure. Obviously the use of fresh material for alkaloidal poisons is preferred.

ACID DISTILLATE		ALKALINE DISTILLATE
Hydrocyanic acid	Formaldehyde	Amines
Chloroform	Carbon disulfide	Ammonia
Ethyl alcohol	Acetone	Chloroform (see chloral hydrate)
Methyl alcohol	Turpentine	
Nitrobenzene	Iodine	Aniline
Iodine (free)	Phosphorus	Volatile alkaloids
Iodoform	Cresols	Nicotine
Benzene	Carbon tetrachloride	Coniine
Phenol	Other volatile substances	Other volatile bases
Chloral hydrate		

Nonvolatile Organic Compounds

(Above residue, acidified, may be used, or acidify 100 Gm. fresh tissue with tartaric acid.)

BASIS OF SEPARATION.—The separation depends on the fact that glucosides and alkaloid salts are soluble in alcohol or aqueous alcohol. Glucosides are extracted from an aqueous or acid solution by chloroform or ether, while alkaloid salts are not. Free alkaloids, liberated by alkali, are soluble in chloroform and other organic solvents.

Extract four times with 200 cc. of 50 per cent ethyl alcohol, using a reflux condenser, cool, and filter. Evaporate combined alcoholic extracts (under vacuo) over hot water bath to syrupy consistency. Add 100 cc. of 95 per cent alcohol, warm, then cool (icebox) and filter. Evaporate filtrate as before to a syrupy consistency, add 75 cc. of absolute alcohol, warm, cool again in icebox, filter. Evaporate filtrate to a few cubic centimeters over a water bath, add 5 cc. of 50 per cent sulfuric acid, stir and add 150 cc. of distilled water. Warm on water bath, place in refrigerator to allow separation of lipoids. Filter. The filtrate (A) is ready for extraction of the nonvolatile organic compounds (B + C).

(B) NONALKALOIDAL POISONS	(C) ALKALOIDAL POISONS
[Extract (A) with 25, 15, 10 cc. portions of ether in 250 cc. separatory funnel. Test ether extract for poisons listed below.]	(The acid aqueous solution remaining after extraction with ether is now made alkaline with MgO. Extract with chloroform in the same proportions as with ether. Test chloroform extract for alkaloids.)
Acetanilid	Strychnine
Acetophenetidin	Brucine
Antipyrine	Nicotine
Aminopyrine	Cocaine
Barbital	
Phenobarbital	

Salicylic acid and derivatives	Procaine
Sulfonal, trional, tetronal	Quinine
Caffeine	Atropine
Theobromine	Codeine
Theophylline	Apomorphine
Other nonalkaloidal poisons	Morphine
	Diacetyl morphine
	Other alkaloids

Note: The above ether and chloroform extracts may be purified by evaporating to dryness, dissolving in water, and again extracting with appropriate solvent. Test ether (or chloroform) extract by allowing several drops of fluid from separatory funnel to evaporate on a white porcelain crucible cover. Then apply appropriate tests. Precipitation and color tests are commonly employed. See tests as described in standard textbooks on detection of poisons.

RAPID SEPARATION METHOD.—In order to circumvent the usually tedious and lengthy separation methods and to avoid loss of poisonous sustances, the following method may be resorted to sometimes with advantage. The minced tissue or residue remaining after removal of volatile substances is extracted with its own weight of 20 per cent trichloroacetic acid solution and the mixture is filtered. Fuller's earth, or kaolin, may be added to the filtrate to adsorb the alkaloids. The Fuller's earth, or kaolin, is then treated with sodium bicarbonate, dried, and extracted with chloroform which dissolves the free alkaloids.

Metallic Poisons

For the detection and estimation of metallic poisons various procedures are employed. A complete analysis for all possible metals is rarely indicated, as it would be superfluous to test for nonpoisonous metals. Those metals of special importance toxicologically include arsenic, antimony, barium, bismuth, mercury, lead, silver, thallium, tellurium, cadmium, and possibly others.

The Reinsch test should be carried out if metallic poisoning is suspected. *Actually, the Reinsch test is very generally used as a preliminary measure in any case of poisoning of unknown origin.*

To test for metallic poisons 100 Gm. of fresh tissue may be used, or if the amount of material is small the residue remaining after examining for volatile poisons and the members of the nonvolatile group of organic compounds may be used. Before testing the organic matter most of the food or tissues must be destroyed. The most rapid method is by ashing. However, some poisons, such as arsenic, lead, mercury, and zinc, suffer a loss by volatilization during ashing; it is not the method of choice. The method of preference for the destruction of organic matter is digestion by means of strong oxidizing agents, such as perchloric and sulfuric acids. Micromethods of analysis have been perfected to such a degree in recent years as to be of great value.

STANDARD TOXICOLOGICAL TESTS

The following simple tests should solve the great majority of toxicological problems occurring in the average medicolegal practice.

Volatile Poisons

While odor, appearance, etc., may aid in the recognition of volatile poisons in the distillate, the final decision must rest on chemical tests.

Ethyl Alcohol

Ethyl alcohol is usually found in the first fraction of the distillate. Test odor, and apply chemical tests.

1. *Lieben's Iodoform Test.*—To a few cubic centimeters of distillate add 5 drops of 10 per cent KOH solution, heat in warm water for five minutes. Add, drop by drop, iodine solution (iodine 5 per cent, potassium iodide, 10 per cent) till the liquid takes on a permanent brown tint. Add carefully more 10 per cent potassium hydroxide solution until color disappears. There is a characteristic odor of iodoform if ethyl alcohol is present. The test is also positive for aldehydes, acetone, and other alcohols.

2. To 2 cc. of distillate add 2 Gm. of dry sodium acetate and a few cubic centimeters of concentrated sulfuric acid, and warm. Traces of ethyl alcohol in distillation causes the characteristic odor of ethyl alcohol.

Quantitative Estimation of Ethyl Alcohol.—Arrange three large test tubes in series, two of which are immersed in a water-bath (80° C.), the third being connected to a suction pump to draw air through the apparatus. Place concentrated sulfuric acid in the first tube to wash the air. Place 2 cc. of blood or urine, or 2 Gm. of suspected ground tissue in the second. In the third, place 10 cc. of N/10 potassium bichromate (4.903 Gm. per liter) and 10 cc. of concentrated sulfuric acid.

The air current is started, the alcohol volatilizes, is carried through the oxidizing mixture, and is absorbed and oxidized. Continue passage of air current for approximately one hour. Next, transfer carefully the bichromate mixture and washings to a volumetric 500 cc. flask and make to volume. Add 5 cc. of 0.4N potassium iodide (51.2 Gm. per 1,000 cc.) a few drops of starch solution, then titrate with N/10 sodium thiosulfate (24.82 Gm. of $Na_2S_2O_3.5H_2O$ per 1,000 cc.) until the deep blue color just disappears.

Calculations: Let us say 6.10 cc. were used in titration; therefore, 10 - 6.10 cc., or 3.90 cc. of bichromate were used by the alcohol. Since each cubic centimeter of N/10 bichromate solution is equivalent to 1.15 mg. of alcohol, then since 2 cc. of blood or urine were used, the alcohol in milligrams per 10 cc. is

$$57.5 \times 3.90 \text{ or } 224.25$$

Where the amount of material available is very limited, one of the micromethods is indicated.

Methyl Alcohol

Methyl alcohol is found in the first part of the distillate. Oxidize the methyl alcohol by distilling with potassium dichromate and sulfuric acid. Collect the formaldehyde by distillation in a well-cooled receiver. Test for formaldehyde as given below.

Deniges Method.—Reagents: One per cent of $KMnO_4$ solution, concentrated sulfuric acid, 10 per cent oxalic acid solution, Schiff's reagent (dissolve 0.2 Gm. of basic fuchsin in 120 cc. of hot distilled water, cool, and add 2 Gm. of sodium bisulfite (meta) in 20 cc. of water. Add 2 cc. of concentrated hydrochloric acid and dilute with distilled water to 200 cc. Allow to stand for one hour before use. This solution will keep for two weeks.

Procedure: Place 5 cc. of distillate (obtained same as for ethyl alcohol) in a test tube, add 2.5 cc. of $KMnO_4$ solution (1 per cent) and 0.2 cc. of concentrated H_2SO_4. After three minutes add 0.5 cc. of oxalic acid solution. Now add 1 cc. of concentrated sulfuric acid, mix and add 5 cc. of Schiff's reagent. In the presence of methyl alcohol

a distinct blue or violet color appears within ten minutes. (Since this test depends upon oxidation of methyl alcohol to formaldehyde, tissues fixed in formalin and urine after methenamine medication contraindicate this test.)

Formaldehyde

Carry distillation at low temperature to collect formaldehyde in early fraction of distillate.

Test.—To 0.5 cc. of distillate add a few drops of 5 per cent phenyl hydrazine sulfate solution and one drop of N/10 potassium ferricyanide solution. Layer mixture on surface of concentrated sulfuric acid in a test tube. A positive test for formaldehyde is present if a red color appears at junction of the two layers.

Cyanides

Cyanides pass off during direct distillation from the acid solution. To test for cyanides let distillate bubble through a test tube containing 10 cc. of dilute alkali for a few minutes. Apply the following tests:

Schönbein's Test.—Reagents: Guaiac-copper paper (saturate strips of filter paper with freshly prepared 10 per cent alcoholic solution of gum guaiac). Dry and moisten with 0.1 per cent solution of copper sulfate.

Procedure: Acidify (to litmus) material to be tested (first stomach washings, etc.) in a flask with tartaric acid solution. Close flask, suspend guaiac-copper paper through slit in stopper. Gently warm flask in water bath. Paper turns blue in presence of cyanide. *Note:* A negative test rules out cyanide. If test is positive, confirm it by the following test, as other substances also produce a blue color.

Prussian Blue Test.—Reagents: Ten per cent solution of ferrous sulfate, 10 per cent solution of ferric chloride, 10 per cent solution of NaOH, and dilute HCl (5 cc. of concentrated HCl plus 5 cc. of distilled water).

Procedure: Test steam distillate from acidified material (as for ethyl alcohol). Test first 5 cc. of distillate. Make alkaline by adding several drops of 10 per cent NaOH. Add 0.5 cc. of ferrous sulfate solution and 0.5 cc. of ferric chloride solution. Shake well and warm. Acidify (to litmus) with dilute HCl solution. A positive test for cyanide is indicated by the formation of a blue color or of a precipitate.

Phenol

Phenol passes into the first part of the distillation from the acid solution. Note if any characteristic odor of phenol is present. Acidify a portion of the distillate with sulfuric acid and extract with ether. Allow ether to evaporate and apply the following tests.

Millon's Test.—Reagent: *Millon's* reagent.—Dissolve 10 Gm. of mercury in 10 Gm. of concentrated nitric acid, warm gently and dilute with twice its value of distilled water. After it has stood for several hours, decant clear solution for testing.

Procedure: Add 2 cc. of Millon's reagent to 2 cc. of distillate and heat gently. A positive test is indicated by a red color. (Aniline, salicylic acid, tyrosine, etc., also give a positive Millon's test.)

Ferric Chloride Test.—Reagent: Forty per cent ferric chloride solution.

Procedure: Add, drop by drop, ferric chloride solution to 5 cc. of distillate. If phenol is present, a blue violet color occurs. (Mineral acids and alcohol will prevent the color reaction.)

PHOSPHORUS

Mitscherlich's Method.—Connect a large flask by means of a two-angle glass tube to a condenser, in a vertical position. Drop lower end of condenser into 5 cc. of water in a small flask. Fill large flask one-third with material to be tested. Acidify with tartaric acid. Heat flask to boiling. When boiling point is reached, darken room and look for a luminous ring in the upper part of condenser. This ring is a positive test for yellow phosphorus.

Note: This trustworthy test for phosphorus depends upon the separation of free phosphorus in a current of steam where it phosphoresces. The presence of certain volatile substances such as alcohol, ether, chloroform, and phenol prevent phosphorescence as long as they continue to distill, while turpentine oil and some essential oils completely inhibit it.

Scherer's Test.—REAGENT: Ten per cent silver nitrate solution.

PROCEDURE: Place material to be tested in a small flask and acidify with tartaric acid. In the neck of the flask suspend a strip of filter paper moistened with silver nitrate solution so that it will touch the walls of the flask. Warm (40° C.) gently in water bath. If paper is not darkened, phosphorus can be excluded. If the paper is darkened, yellow phosphorus may be present and Mitscherlich's test indicated.

Scherer's test is a good preliminary but not specific. It at least indicates the absence of phosphorus. It is desirable to apply other tests.

Nonvolatile Organic Compounds

BARBITURATES

Koppanyi's Test.—REAGENTS: Cobaltous acetate solution (dissolve 0.5 Gm. of cobaltous acetate in 100 cc. of absolute methyl alcohol), isopropylamine solution (dissolve 5 cc. of isopropylamine (Eastman Kodak Co.) in 100 cc. of absolute methyl alcohol). Keep this solution in refrigerator.

PROCEDURE: Place in a test tube 2 cc. of ether extract of acid solution (B). Add 0.2 cc. of cobaltous acetate solution, followed by 0.6 cc. of isopropylamine solution. If barbiturates are present, the ether will assume a pinkish violet color.

STRYCHNINE

Strychnine resists putrefaction and is one of the most stable alkalies. After extraction and purification, taste the extract. A dilution as low as 1:70,000 will give a bitter taste.

Fading Purple Test.—REAGENTS: Concentrated sulfuric acid, crystals of potassium bichromate.

PROCEDURE: Evaporate 5 cc. of chloroform extract (C) to dryness in a porcelain dish. Dissolve residue in 0.5 cc. of concentrated sulfuric acid. Drop in a small crystal of potassium bichromate. The formation of a play of colors from blue to violet to purple red and finally to orange or yellow, on drawing through the liquid a small crystal of potassium dichromate is a positive test for strychnine.

The sequence of color is important. Large excess of morphine or brucine interferes with the reaction. Gelsemine and curarine gives similar but not identical colors.

Biologic Test.—Inject some of the extract into the dorsal lymph sac of a frog. If strychnine is present, a general tonic spasm will be observed. A quantity of 0.04 mg. should produce response in ten to thirty minutes.

Mandelin's Test.—Add 2 drops of Mandelin's reagent (ammonium vanadate, 1 per cent, in concentrated sulfuric acid) to some residue

containing strychnine. A blue coloration is formed which changes to a brilliant violet. The addition of ammonium hydroxide changes it to rose red. The test is especially useful for detection of small amounts of strychnine.

Morphine and Morphine Derivatives

The Marquis test is a most useful negative test. If the color is not obtained, there probably is no morphine present; if it is obtained, confirm by other tests; of these the apomorphine reaction is recommended.

Marquis Test.—Reagent: Marquis reagent (3 cc. of concentrated sulfuric acid plus 2 drops of 40 per cent formaldehyde). Prepare at time of test.

Procedure: Evaporate 10 cc. of chloroform extract (C) to dryness and add 3 drops of Marquis reagent. Morphine gives an intense purple-red color, changing to violet, and then blue. This reaction is quite distinctive and accurate to 0.02 mg. With this reagent, codeine and apomorphine give a violet purplish-red color. Oxydimorphine shows a green, changing to flame red. Dionine shows a dark blue violet. Heroin and morphine give similar colors.

Apomorphine Reaction.—Moisten residue with pure concentrated sulfuric acid, allow to stand twenty-four hours in a desiccator, then add 1 drop of concentrated nitric acid. A red-violet color appears changing to dark blood-red and then to yellow-red. A crystal of potassium nitrate may be substituted for the nitric acid.

Metallic Poisons

A Reinsch Test should be carried out, before starting the distillation, on fresh viscera, vomitus, etc. It is a most convenient and valuable test for arsenic, mercury, antimony, bismuth, and other inorganic poisons.

Reinsch Test.—Reagents: Concentrated HCl and pure copper foil. Wash 1 sq. cm. of copper foil in concentrated HNO_3, rinse in distilled water. Handle only with forceps.

Procedure: Place urine, stomach contents, or about 25 Gm. of minced tissue, the latter mixed with 25 cc. of water, in a beaker and add one-sixth of its volume of concentrated HCl. *Note:* If urine or stomach washings are used, concentrate 200 cc. (made alkaline with NaOH) to about 40 cc. Acidify with 6 cc. of concentrated HCl. Then apply test. Suspend copper foil in mixture, heat contents slowly to boiling point and boil gently for five minutes, with stirring. Set aside for thirty minutes, then examine copper foil for deposits. Mercury produces a silvery deposit, arsenic a grayish black, and antimony a black deposit.

The foil is removed, washed, dried, and introduced into a small sublimation tube (McNally tube). Gentle heat is applied and the arsenic is volatilized, and forms small crystals of arsenous oxide just beyond the heated area or constriction of tube. Under the microscope numerous octahedral crystals are deposited. The test is sensitive to 0.25 mg. arsenic per 50 cc. of fluid. Antimony sublimes and leaves an amorphous deposit. Mercury is deposited in the constriction as small globules of mercury which are easily seen under a microscope. Bismuth does not sublime. The test cannot be applied in the presence of chlorates or nitrates, and may fail if arsenic is present in organic forms. ***For clinical use, the rapidity with which this test can be conducted makes it of value to the physician.***

Gutzeit's Test for Arsenic.—If very small amounts of arsenic are present use Gutzeit's test.

REAGENTS: Pure zinc, 6 per cent sulfuric acid, Gram's iodine solution, silver nitrate solution (1:1).

PROCEDURE: Place 1 Gm. zinc in a large test tube, add 5 cc. of 6 per cent H_2SO_4. Add three drops of Gram's iodine to remove hydrogen sulfide or sulfurous acid. Add 5 cc. of unknown and cover test tube with three layers of filter paper. Moisten upper layer with a drop of silver nitrate. Set tube aside for thirty minutes in a dark place. A positive test for arsenic is evidenced by a yellow stain on the top filter paper which turns black when a drop of water is added to the stain.

Gaseous Poisons

CARBON MONOXIDE

Pyrotannic Acid Test.—REAGENT: Pyrotannic acid. Dissolve 1 Gm. of pyrotannic acid and 1 Gm. of tannic acid in 100 cc. of distilled water.

PROCEDURE: Place 1 cc. of blood in test tube, add 9 cc. of distilled water and 10 cc. of pyrotannic acid reagent. After standing fifteen minutes, if carbon monoxide is present the blood will retain a pink color. With normal blood the original pink color will change to a grayish brown. (Will detect CO in embalmed bodies.)

Hoppe-Seyler's Sodium Hydroxide Test.—REAGENT: Concentrated NaOH.

PROCEDURE: Mix two drops of blood to be tested with three drops of concentrated NaOH in a white porcelain dish. A positive test is evidenced by the formation of a red precipitate, while normal blood forms a greenish-brown mass.

POINTS OF TOXICOLOGICAL SIGNIFICANCE

Absorption of Poisons.—The examination of the visceral organs, brain, and blood is indicated, inasmuch as the presence of a poison in these tissues indicates that it has been absorbed into the body. Analysis of the stomach contents is important from the standpoint of identifying a poison, but it does not indicate the amount absorbed in the body. Furthermore, one must keep in mind that some poisons, such as morphine, mercury, and sodium fluoride, are reabsorbed by the stomach.

Signs and Symptoms at Death Important.—If the fatal attack was ushered in by sudden syncope and almost instant death *cyanides* would be looked for. *Strychnine* would be thought of if convulsive seizures preceded death. If death was preceded by unconsciousness and somnolence, an overdose of *alcohol* or *barbiturates* might be the cause. Gastrointestinal upset, followed by circulatory collapse and death, is characteristic of poisoning by *heavy metals, fluoride,* or *nicotine.*

A Poison May Be Undetectable.—Certain poisons which cause death may escape detection. Good methods for chemical detection may not be available; poisons may be removed by purging or vomiting; and absorption may be so slight that none will be found in the vital organs. Certain poisons may be sufficiently modified in the body to escape detection.

Quantity of Poison Absorbed Important.—A quantitative determination of the poison may be essential in evaluating the role of toxic substance with regard to death. If the patient has been taking drugs, no doubt small quantities could be detected, yet not be the cause of fatal poisoning.

A positive qualitative test for arsenic in gastric washings might satisfy the clinician handling the case, but if such evidence was presented

in court it surely would be discredited by the defendant who could show: (1) that small amounts of arsenic may come from sources other than those presented by the State, (2) that very small amounts of arsenic may give a positive test, and (3) that demonstration of arsenic in the stomach does not necessarily prove that death was due to arsenic poisoning.

Common Poisons.—Statistical tables show that alcohol, illuminating gas, carbon monoxide, phenol, cyanides, barbiturates, lysol, lye, arsenic, mercury, paraldehyde, morphine, lead, strychnine, chloral hydrate, antimony, barbital, salicylates, arsphenamine, iodine, in the order listed, are substances that are commonly associated with poisoning; they are the poisons that deserve first consideration from the toxicologist if the substance causing the poisoning is unknown. Many substances other than those listed, although of less importance toxicologically, frequently must be tested for.

If alcohol, carbon monoxide, and barbiturates have been excluded, it then may be advisable to test for heavy metals, and for fluoride, cyanide, nicotine, and strychnine. Obviously the exclusion of these poisons does not exhaust the possibilities that death was due to poisoning. It is questionable, however, if there would be justification for extending the search much farther in a case exhibiting no positive evidence of poisoning.

Interferences With Toxicological Examination.—Many conditions interfere with the toxicological examination. Embalming may void the test for many volatile poisons and may interfere with the extraction of many organic compounds. Post-mortem decomposition interferes with the tests for volatile substances like alcohol, and makes identification of alkaloids unreliable due to the formation of ptomaine-like substances which give identical tests. The destruction of the body by strong chemicals, such as strong mineral acids and strong alkalies, interferes with the toxicological examination, except in the case of a few inorganic poisons.

One of the various agents that should be expected in obscure deaths is alcohol, either ethyl or methyl. The interval between ingestion of alcohol and death is frequently so long that little or no alcohol will be recovered by the analyst. Fatal poisoning may also occur without significant gross or microscopic changes in the tissues. The barbitals may also be destroyed by the time autopsy is performed and yet be the cause of death.

Interpretation of Results.—Many perplexing problems face the toxicologist in interpreting the results of his analysis. The question arises as to whether or not the condition could be produced artificially in the body. Embalming with fluid containing arsenic nullifies the value of an arsenic determination. Poisons placed in the body after death slowly diffuse through the tissues and simulate poisoning before death. Persons dying of carbon monoxide poisoning may give negative toxicological tests after twenty-four hours. Likewise, the organs of a person poisoned by phosphorus, and living for several days, may give a negative determination for phosphorus.

In order to understand and determine the part played by the poison in causing death, the results of the analysis should be studied in relation to the duration of the victim's ills, the pathological lesions, the symptoms presented, and other available information.

References

Autenreith, W.: Laboratory Manual for the Detection of Poisons and Powerful Drugs, Philadelphia, 1928, P. Blakiston's Son and Co.

Blythe: Poisons, Their Effect and Detection, ed. 5, London, 1920, Charles Griffin and Co.

Brundage: A Manual of Toxicology, ed. 15, New York, 1931, D. Appleton-Century Co.

Dack, G. M.: Food Poisoning, Chicago, 1943, The University of Chicago Press.

Davison, F. R.: A Manual of Toxicology, New York, 1939, The Paul B. Hoeber Co.

Glaister, John: Medical Jurisprudence and Toxicology, ed. 7, Baltimore, 1942, William Wood and Co.

Glaister, John, and Brash, J. C.: Medico-Legal Aspects of the Ruxton Case, Baltimore, 1937, William Wood and Co.

Gonzales, T. A., Helpern, M., and Vance, B. M.: Legal Medicine and Toxicology, New York, 1937, D. Appleton-Century Co.

Hamilton, Alice: Industrial Toxicology, New York, 1934, Harper and Brothers.

Hamilton, Alice, and Johnstone, R. T.: Industrial Toxicology, New York, 1945, Oxford University Press.

Leschke, Erich: Clinical Toxicology, Baltimore, 1934, William Wood and Co.

McNally, W. D.: Medical Jurisprudence and Toxicology, Philadelphia, 1939, W. B. Saunders Co.

Medical Manual of Chemical Warfare (Reprinted by permission of the controller of His Britannic Majesty's Stationery Office), Brooklyn, 1941.

Peterson, Haines, and Webster: Legal Medicine and Toxicology, Philadelphia, 1923, W. B. Saunders Co., Vol. II.

Physician's Reference Book of Emergency Medical Service, New York, 1942, E. R. Squibb and Sons.

Sappington, C. O.: Essentials of Industrial Health, Philadelphia, 1943, J. B. Lippincott Co.

Smith, Sidney: Forensic Medicine, ed. 8, London, 1943. J. & A. Churchill.

Stekol, J. A.: Detoxication Mechanisms, In Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Annual Reviews, Inc., 1941, vol. 10, pp. 265-284. Handler, P., and Perlziveig, W. A.: Detoxication Mechanisms, ibid., 1945, vol. 14, pp. 617-642. Williams, R. T.: Detoxication Mechanisms: The Metabolism of Drugs and Allied Organic Compounds, New York, John Wiley & Sons, Inc., 1948.

U. S. Army Manual, Chemical Warfare Bulletin, Vol. 27, No. 1, Jan., 1941, and No. 3, July, 1941.

Wampler, F. J.: Principles and Practice of Industrial Medicine, Baltimore, 1943, The Williams and Wilkins Co.

Webster, Ralph W.: Legal Medicine and Toxicology, Philadelphia, 1930, W. B. Saunders Co.

PART II

CLASSIFICATION OF DRUGS

I. Vehicles
- A. Flavoring Vehicles
- B. Coloring Vehicles
- C. Solid and Semisolid Vehicles
- D. Excipients

II. Drugs Acting on Skin and Mucous Membranes
- A. Emollients
- B. Demulcents
- C. Protectives
- D. Irritants
- E. Astringents
- F. Caustics
- G. Carminatives
- H. Bitters
- I. Gastric Antacids
- J. Digestants
- K. Emetics
- L. Expectorants
- M. Adsorbents
- N. Cathartics

III. Antiseptics, Disinfectants, and Anti-infectives

A. Antiseptics and Disinfectants
1. Phenol Derivatives
2. Mercury and Mercury Derivatives
3. Silver Compounds
4. Oxidizing Agents
5. Acids
6. Volatile Oils
7. Dyes
8. Iodine and Iodine Compounds
9. Chlorine Derivatives
10. Spermatocides
11. Industrial Skin Cleansers
12. Detergents
13. Miscellaneous
    - a. Betanaphthol
    - b. Ichthammol
    - c. Benzyl Benzoate
    - d. Resorcinol
    - e. Hexylresorcinol
    - f. Sulfur
    - g. Sulfurated Potash
    - h. DDT
    - i. Nitrofurazone

B. Anti-infectives
1. Sulfonamides
2. Antibiotics
    - a. Penicillin
    - b. Streptomycin
    - c. Tyrothricin
    - d. Polymyxin
    - e. Other Antibiotic Agents
3. Anthelmintics
    - a. Oleoresin of Aspidium
    - b. Carbon Tetrachloride
    - c. Tetrachloroethylene
    - d. Hexylresorcinol
    - e. Chenopodium Oil
    - f. Gentian Violet
    - g. Santonin
    - h. Tartar Emetic
    - i. Stibophen
    - j. Neostibosan, etc.

4. Amebecides
   a. Ipecac
   b. Emetine
   c. Emetine Bismuth Iodide
   d. Chiniofon
   e. Iodochlorhydroxyquinoline
   f. Diiodo-oxyquinoline
   g. Carbarsone, etc.
5. Antisyphilitic Drugs
   a. Organic Arsenicals
   b. Bismuth Preparations
   c. Mercury Preparations
   d. Iodides
   e. Penicillin
6. Antimalarial Drugs
   a. Quinine
   b. Totaquine
   c. Quinacrine
   d. Pamaquine
   e. Chloroquine
   f. Paludrine
   g. Pentaquine
   h. Chlorguanide Hydrochloride
7. Miscellaneous
   a. Methenamine
   b. Mandelic Acid and Salts
   c. Chaulmoogra Oil
   d. Sulfones
      (1) Promin
      (2) Diasone
      (3) Promizole

IV. Drugs Acting on the Central Nervous System

A. Stimulants of C.N.S.

1. Cerebrum:
   The Caffeine Group
2. Medulla:
   Apomorphine, Picrotoxin, Metrazol, Nikethamide
3. Spinal Cord:
   The Strychnine Group

B. Depressants of C.N.S.

1. General Anesthetics:
   Ether, Chloroform, Nitrous Oxide, Ethylene, Ethyl Chloride, Cyclopropane, Tribromoethanol, Vinyl Ether, Adjuvants (Curare, Oxygen, Carbon Dioxide)
2. Intravenous Anesthetics:
   Thiopental Sodium, Hexobarbital Sodium
3. Hypnotics:
   Paraldehyde, Chloral Derivatives, The Sulfone Group, Barbituric Acid Derivatives
4. Sedatives:
   Bromides and Compounds Containing Bromine, Cannabis, Scopolamine (Hyoscine), Hydantoin Derivatives, Trimethadione (Tridione)
5. Analgesics:
   Opium, Morphine, Codeine, Papaverine, Narcotine, Thebaine, Pantopon, Heroin, Dionin, Apocodeine, Apomorphine, Dihydromorphinone Hydrochloride (Dilaudid), Demerol (Isonipecaine), Methadon
6. Antipyretics:
   Acetanilid, Acetophenetidin, Antipyrine, Aminopyrine, Salicylic Acid Derivatives, Cinchophen, Neocinchophen, Colchicine, etc.
7. Alcohols:
   Ethyl, Methyl, Isopropyl

V. Drugs Acting on Peripheral Nervous System

A. Drugs Acting on Autonomic Nervous System

1. Parasympathetic

a. Stimulants:

Acetylcholine, Pilocarpine, Physostigmine, Neostigmine (Prostigmine), Carbachol (Carbaminoylcholine), Di-isopropyl Fluorophosphate ("DFP"), Choline, Muscarine

b. Depressants:

Atropine, Scopolamine, Hyoscyamine, Strammonium, Homatropine, Eucatropine Hydrochloride, Homatropine Methylbromide, Eumydrine

2. Sympathetic

a. Stimulants:

Epinephrine, Ephedrine, Amphetamine (Benzedrine), Phenylephrine Hydrochloride (Neosynephrine), Kephrine, Paredrine, Propadrine Hydrochloride, Naphazoline Hydrochloride (Privine), Tuamine, Vonedrine, Tyramine

b. Depressants:

Ergotoxine, Ergotamine, Yohimbine, Dioxane Derivatives

3. Sympathetic and Parasympathetic Ganglia

Nicotine, Lobeline, Coniine, Gelsemine, Tetraethylammonium Chloride

B. Drugs Acting on Cerebrospinal Nervous System

1. Local Anesthetics:

Cocaine, Butesin Picrate, Butyl Aminobenzoate, Ethyl Aminobenzoate, Orthoform, Amylsine Hydrochloride, Butacaine Sulfate, Diothane, Phenacaine, Procaine, Monocaine, Tutocaine, Amydricaine, Benzyl Alcohol, Metycaine, Tetracaine, Dibucaine Hydrochloride

VI. Cardiovascular Drugs

The Digitalis Group (Digitalis Leaf Preparations, Digitoxin, Digoxin, Lanatosid-C), Ouabain, Strophanthin, Quinidine, Papaverine, Xanthine Derivatives, Thiocyanates

VII. Oxytocic Drugs

Ergot, Ergonovine, Pituitrin, Pitocin, Quinine

VIII. Diuretics

A. The Mercurials

Mersalyl (Salyrgan), Mersalyl and Theophylline, Mercurophylline, Meralluride Sodium Solution

B. The Caffeine Group

C. Saline Group

D. Miscellaneous

Urea, Glucose, Sucrose, Water

IX. Biologicals

A. Vitamins

B. Serums and Vaccines

C. Blood, Blood Derivatives and Substitutes

Whole Blood, Human Plasma and Serum, Serum Albumin, Globulins, Thrombin, Fibrinogen and Fibrin, Red Blood Cells, Colloidal Solutions (Gelatin, Pectin, Polyvinyl Alcohol, Acacia, Dextran)

D. Hematinics

Iron and Iron Compounds, Liver and Stomach Preparations, Folic Acid, Heparin, Dicumarin, Blood Coagulants, Sclerosing Agents, Pentnucleotide, Radioactive Phosphorus, Phenylhydrazine, Urethane, Arsenic, Nitrogen Mustards

E. Hormones

X. Miscellaneous

Histamine and Antihistamine Drugs, Protein and Amino Acid Preparations, Snake Venom, Rhus Preparations, Arsenic, Fluorides, Helium, Gold

CHAPTER V

DRUGS ACTING ON SKIN AND MUCOUS MEMBRANES

1. EMOLLIENTS, DEMULCENTS, PROTECTIVES, IRRITANTS, ASTRINGENTS

Emollients, demulcents, and protectives are chemically inert substances used chiefly to cover and thus protect the skin from external irritants. They act locally in a purely mechanical or physical manner.

Emollients (L. *emollire,* to soften) are chiefly bland, oily substances, such as fats, oils, and glycerin. They are employed as vehicles for more active drugs, for softening and rendering skin more pliable, and as protectives. In the former case, they may serve as vehicles for drugs having as their chief purpose a *local* action in which it is desirous of maintaining a slow liberation of the drug from the base; or they may serve as vehicles for drugs from which absorption and systemic effects are desired. In this case the ointment should be rubbed in to insure absorption through the sebaceous glands.

Demulcents (L. *demulcere,* to smooth down) are mucilaginous substances, such as gums, dextrins, and starches, which form colloid-like solutions in water. They are used to (1) allay inflammation, (2) delay absorption of other drugs, (3) mitigate taste, (4) protect against irritant poisons, and (5) to emulsify oils and suspend insoluble substances.

1. Demulcents *allay inflammation* when they are applied over inflamed surfaces; in tonsillitis they may be used as gargles or administered by sucking lozenges containing demulcent principles.

2. Their effect in *delaying absorption* of other drugs may be illustrated by opium, which is prescribed when local action on the bowel or stomach is desired, while the pure alkaloid morphine is administered for its effect after absorption.

3. *The taste of food is altered* by demulcents, although demulcents are relatively tasteless and odorless. Sugar dissolved in mucilage tastes less sweet than when dissolved in water, acids in mucilages taste less acid, and ice cream less cold than ice. Large quantities of fluid may be administered with greater ease in the form of demulcents, since they are more agreeable to the taste, e.g., barley water.

4. *Protection against irritant poisons* is afforded by demulcents. They act by retarding absorption and by protecting the walls of the stomach from the effects of the poisons.

5. Demulcents are used to *emulsify oils,* such as emulsified cod-liver oil, and to make a more permanent suspension of insoluble substances, thus making medication easier and more accurate. Gum acacia and tragacanth are especially adapted to holding substances in suspension, such as resins or oils, and giving cohesion to pills and lozenges.

The most important demulcents are: acacia, tragacanth, starch, flaxseed, glycyrrhiza or licorice root, agar, almond, and glyceryl monostearate.

Protectives are chemically inert substances used to protect wounded or inflamed surfaces of the skin and mucous membranes against external irritation. The external irritation may be due to drying, or to the access of bacteria and mechanical irritants.

EMOLLIENTS OR OILY AND FATTY SUBSTANCES

Lard

Lard, the purified internal fat of the abdomen of the hog, is a cheap and easily accessible fat composed chiefly of stearin, palmitin, and olein. *Benzoinated lard* is a soft, white solid containing the soluble constituents of 1 per cent of benzoin, added in an attempt to preserve it, conceal its odor, and give it antiseptic and stimulating properties.

Action and Uses.—Lard and Benzoinated Lard are rarely used alone as emollients but are chiefly used as the basis for ointments carrying healing, softening, stimulant, anodyne, or antiseptic drugs. They have some ability to penetrate into the skin and are well adapted to being applied with friction. They have the ability to absorb about 2 per cent water. They are liable to become rancid if kept too long.

Petrolatum

Petrolatum, also called paraffin and petroleum jelly, is a non-volatile, inactive mixture of semisolid hydrocarbons obtained from petroleum. It is insoluble in water and in alcohol, but soluble in fats and fat solvents.

Action and Uses.—Petrolatum possesses emollient, lubricant, and laxative action. It is used chiefly as a lubricant and vehicle. It has the disadvantage of not mixing with water. It apparently possesses slight ability to penetrate into the skin and thus is used as a vehicle for medicaments intended to act on the surface of the skin. Liquid Petrolatum is employed extensively as a laxative and to some extent as a vehicle. Heavy and light mineral oils are available.

White Ointment, *Unguentum Album*, consists of 90 per cent white petrolatum, 5 per cent white wax and 5 per cent wool fat. It is used alone to allay skin irritation or as a basis or vehicle for carrying other remedies.

Yellow Ointment, *Unguentum Flavum*, contains wool fat, 5 per cent, yellow wax, 5 per cent, in petrolatum, 90 per cent. It is used as an ointment base.

Glycerin

Glycerin, $C_3H_5(OH)_3$, is a clear, colorless, odorless, syrupy, sweetish liquid, obtained by the hydrolysis of animal and vegetable fats and purified by distillation. Chemically it is a tri-atomic alcohol. When exposed to air it absorbs moisture. It is freely soluble in water and alcohol; insoluble in ether, chloroform, and oils. Glycerin solutions of medicinal substances are known as glycerites.

Pharmacological Action.—Glycerin acts chiefly as an emollient and demulcent. It abstracts water from irritated, inflamed, chapped surfaces of the skin and mucous membranes. When applied to normal skin it does not abstract water, on account of the impermeability of the stratum corneum (Sollmann). On diseased surfaces its soothing action is preceded by smarting, due to extraction of water.

Therapeutic Uses.—Glycerin is largely used as a vehicle, solvent, and sweetening agent. Its hygroscopic action is taken advantage of in compounding preparations for external application and for preparations, such as *tampons, suppositories, enemas*, etc. Its continued use as tampons and suppositories is contraindicated. When employed on vaginal tampons either the pure glycerin or the boroglycerin is used. These tampons are used in such conditions as pelvic infection, eroded cervix, etc.

Externally, it is extensively employed in ointments and lotions for skin diseases.

For chapped hands, etc.:

℞

Liquefied Phenol	0.40 cc.	(ℳvj)
Glycerin	10.00 cc.	(f℥iiss)
Alcohol	30.00 cc.	(f℥j)
Rose Water	90.00 cc.	(f℥iij)

M. Sig.: Apply freely.

Theobroma Oil

Theobroma Oil, Cacao Butter, is a fat obtained from the seeds of ***Theobroma Cacao.*** The oil is obtained principally as a by-product in the manufacture of cocoa. It possesses a faint, agreeable odor, and a bland chocolate-like taste. It is insoluble in water or alcohol.

Action and Uses.—Theobroma oil possesses emollient and lubricant action. It is a solid at room temperature and melts at body temperature; because of this property it is a valuable vehicle in the manufacture of suppositories.

Expressed Oil of Almond

This oil is obtained from kernels of varieties of *Amygdalus communis.* It is a fixed oil and is contained in several official preparations.

Action and Uses.—It possesses demulcent and nutritive properties. It is rarely prescribed alone but is used chiefly as a constituent of ointments, salves, and emulsions.

Rose Water Ointment (cold cream) is composed of expressed almond oil (56%), spermaceti (12.5%), white wax (12%), sodium borate (0.5%) and rose water (5%). It is a popular toilet article, being a pleasant emollient for dry skin, "chapped hands," etc. It is a suitable vehicle for more active agents.

Paraffin

Paraffin is a purified mixture of solid hydrocarbons, obtained from petrolatum. It is a white waxy tasteless solid melting at 50° to 57° C., soluble in ether and volatile oils, but insoluble in water or alcohol.

Action and Uses.—Paraffin has many pharmaceutical but few therapeutic uses. It is sprayed or painted on burns or other lesions. It should be applied only to selected cases, as retention of moisture and heat encourages infection. It is used to exclude air and prevent drying and contamination. It is also used for injection for cosmetic purposes, a use which is unsafe, as malignant "paraffinomas" may develop. Paraffin is also used to harden ointments and for impregnation of bandages. *Chlorinated Paraffin* is used as a solvent for dichloramine-T.

Wool Fat (Lanolin)

Lanolin is the purified anhydrous fat of sheep's wool. It contains cholesterin esters and alcohols of the fatty series. It is used almost exclusively in the form of *hydrous wool fat.* It rarely becomes rancid; it is miscible with twice or more its weight of water, thus water-soluble salts can be incorporated with greater ease, producing a smoother ointment.

Action and Uses.—Lanolin possesses emollient action. It is used as a vehicle or base for ointments. It is particularly suitable as an ointment if absorption of the active constituents through the skin is desired. Owing to its sticky consistency it is seldom prescribed alone.

For treatment of dermatitis:

℞

Phenol	0.80 Gm. (gr.xij)
Bismuth Subnitrate	6.00 Gm. (3iss)
Hydrous Wool Fat	8.00 Gm. (3ij)
Zinc Oxide Ointment q.s.	30.00 Gm. (℥j)

Make an ointment
Sig.: Apply locally.

Olive Oil

Olive oil is a pale yellow fixed oil expressed from the ripe fruit of *Olea europaea*. It possesses emollient, laxative, and nutrient properties. It is used in skin diseases, in hyperchlorhydria, as a laxative, as a nutrient, and as a vehicle in pharmacy.

Baby Lotion (The New York Hospital Formulary):

R

Stearic Acid	4.6%
Anhydrous Lanolin	6.3%
Liquid Petrolatum	8.8%
Sesame Oil	1.1%
Olive Oil	1.1%
Triethanolamine	1.7%
Alcohol	1.1%
Distilled water	75.3%

M. Sig.: Apply as directed.

Waxes

Waxes are employed to harden ointment bases. A base composed of lard hardened with wax is known as a *cerate*.

Preparations

Lard, *Adeps*, U.S.P., B.P.
Benzoinated Lard, *Adeps Benzoinatus*, U.S.P., B.P.
Petrolatum, *Petrolatum*, U.S.P. *Paraffinum Molle*, B.P.
Liquid Petrolatum, *Petrolatum Liquidum*, U.S.P. (White Mineral Oil). *Dosage:* 15 cc. (4 fluidrachms). *Paraffinum Liquidum*, B.P.
Liquid Petrolatum Emulsion, *Emulsum Petrolati Liquidi*, U.S.P. Liquid petrolatum (50%) acacia, syrup, vanillin, alcohol, and distilled water. *Dosage:* 30 cc. (1 fluidounce).
Glycerin, *Glycerinum*, U.S.P., B.P. *Dosage:* 4 cc. (1 fluidrachm).
Theobroma Oil, *Oleum Theobromatis*, U.S.P., B.P.
Expressed Almond Oil, *Oleum Amygdalae Expressum*, U.S.P. Oleum Amygdalae, B.P.
Rose Water Ointment, *Unguentum Aquae Rosae*, U.S.P.
Paraffin, *Paraffinum*, N.F., B.P.
Wool Fat, *Adeps Lanae*, U.S.P., B.P.
Hydrous Wool Fat, *Adeps Lanae Hydrosus*, U.S.P., B.P. Wool fat with about 27 per cent of water.
Olive Oil, *Oleum Olivae*, U.S.P., B.P. *Dosage:* 30 cc. (1 fluidounce).

White Wax, *Cera Alba*, U.S.P.
Yellow Wax, *Cera Flava*, U.S.P. (Beeswax)
Spermaceti, *Cetaceum*, U.S.P. A waxy substance from the head of the sperm whale. Used in cerates and cold cream.

DEMULCENTS OR MUCILAGINOUS SUBSTANCES

Acacia

Acacia, gum arabic, is a gummy exudate obtained from the branches of *Acacia Senegal* and other species. It consists mainly of potassium, magnesium, and calcium salts of arabin or arabic acid. It is soluble in water and insoluble in alcohol. Its chief preparation is Acacia Mucilage, a 35 per cent aqueous solution of the gum. Acacia should not be prescribed with strongly alcoholic solutions, lead acetate, ferric salts, or sodium borate.

Action and Uses.—Acacia is an emulsifying agent and a suspending agent for such substances as bismuth subcarbonate, barium sulfate, magnesium oxide, etc. Its colloidal properties and low toxicity have led to its use with sodium chloride as replacement therapy after hemorrhage. Acacia is neither metabolized nor excreted and hence after effects, such as deposits in the tissues, may follow repeated use. Acacia may cause urticaria, anaphylactic shock, etc., usually ascribed to impurities in the gum. In hemorrhage shock, 500 to 1,000 cc. of physiological saline plus 6 per cent acacia may be used by vein, administering 10 to 15 cc. per minute.

Tragacanth

Tragacanth is a gummy exudate from *Astragalus gummifer*, difficultly soluble in water, forming a translucent mucilage or jelly varying in viscosity according to the quantity used. Tragacanth Mucilage is an official preparation consisting of a 6 per cent aqueous gel. Tragacanth is a complex carbohydrate. It is a nongreasy lubricant and is used in lotions, troches, pills, suspensions, and emollients. In the manufacture of emollients it is more suitable than is acacia.

In the treatment of pruritus, protection from air may be obtained by the application of tragacanth lotions. If applied in a thin layer, this lotion dries quickly and leaves a thin protective film.

Tragacanth lotion:

℞

Tragacanth	4.00 Gm.	(℥j)
Glycerin	2.00 cc.	(f℥ss)
Water, q.s. ad	90.00 cc.	(f℥iij)

M. Sig.: Apply locally in thin layer.

Starch

Starch, cornstarch, is a white powder obtained from the grain *Zea mays*. It is odorless, tasteless, and insoluble in water or alcohol. It forms a whitish gelatinous mass when boiled with water.

Action and Uses.—Starch is a protective and diluent agent. It may be used externally as a protective in the form of *dusting powders* or ointments in the treatment of prickly heat, chafing, dermatitis, and other skin conditions. Plain, or prepared by boiling, it is added to *baths* for the relief of itching. Starch water is frequently used for *colon irrigation* for the relief of diarrhea and dysentery. Starch is a valuable antidote for the treatment of iodine poisoning.

In the treatment of prickly heat:

℞

Salicylic Acid	0.60 Gm. (gr.x)
Boric Acid	4.00 Gm. (ʒj)
Zinc Oxide	12.00 Gm. (ʒiij)
Starch	30.00 Gm. (ʒj)

M. Sig.: Apply as directed.

OTHER DEMULCENTS.—Many other drugs are used as demulcents in therapeutics. Among them are:

Agar, *Agar*, U.S.P., B.P. *Dosage:* 4 Gm. (1 drachm).

Althea, *Althaea*, N.F. (Marshmallow Root.)

Linseed, *Linum*, U.S.P.

Compound Senna Powder, *Pulvis Sennae Compositus*, N.F. Senna (18%), washed sulfur (8%), with glycyrrhiza, fennel oil, and sugar. *Dosage:* 4 Gm. (1 drachm).

Elm, *Ulmus*, N. F. (Elm Bark, Slippery Elm).

Troches of Elm, *Trochisci Ulmi*, N.O. (Each troche contains elm, tragacanth, sucrose, and anethol.

Acacia, *Acacia*, U.S.P., B.P. (Gum Arabic).

Tragacanth, *Tragacantha*, U.S.P., B.P. (Gum Tragacanth).

For other preparation of this group see Chapter III.

PROTECTIVES

Collodion

Collodion is a 4 per cent solution of pyroxylin, or cellulose tetranitrate (guncotton) in ether and alcohol. It is a clear, almost colorless syrupy, highly inflammable liquid. It is used chiefly as *Flexible Collodion*, composed of camphor (2%), castor oil (3%), collodion (95%). It is rendered flexible by the camphor and castor oil and does not crack or contract, but does not adhere as well as collodion.

Action and Uses.—On evaporation of the solvent collodion forms a thin film which acts as a protective to small wounds of the skin and mucous membrane. The alcohol-ether solvent assures sterility. Flexible collodion is the basis of medicated forms such as salicylic acid corn cures, tannic acid, etc. Some prescribers may add about 25 per cent castor oil to collodion to render it more flexible and to prevent too rapid evaporation.

For treatment of clavus:

℞

Salicylic Acid	2.00 Gm. (ʒss)
Cannabis Extract	0.60 cc. (gr.x)
Flexible Collodion	15.00 cc. (fʒss)

M. Sig.: Apply to corns twice daily.

Insoluble Bismuth Compounds

The insoluble bismuth salts are used locally as protective and astringent dusting powders for the treatment of wounds and excoriated surfaces. All the insoluble compounds of bismuth used in medicine produce essentially the same effects. The insoluble bismuth compounds are used in x-ray diagnosis.

Mode of Action.—The insoluble bismuth compounds act largely mechanically, as protective and drying dusting powders. Applied to

wounds, they dry the secretions and form a protective covering or scab. Their action is partly mechanical and partly due to a small amount of bismuth that goes into solution, and aids by an astringent and mild antiseptic action. They are quite effective nonirritant intestinal antiseptics.

The most commonly used insoluble bismuth compounds are bismuth subcarbonate and bismuth subnitrate. They answer every purpose; the subcarbonate, however, deserves the preference, since it cannot give rise to nitrite poisoning.

Bismuth Subcarbonate

Bismuth Subcarbonate is an amorphous, nearly insoluble, basic powder, yielding not less than 90 per cent Bi_2O_3. It is incompatible with sulfides, sulfur, acids, and acid salts.

Action and Uses.—In the alimentary tract and on skin it is an emollient, astringent, and antacid. If the stomach is acid in reaction it is in part changed to an insoluble oxychloride; in the large intestine it is changed to the black insoluble sulfide. Constipation may follow its continued use. On the skin it acts as an astringent and by its irritant action as a bleach.

By *oral* administration it is used in the treatment of gastritis, hyperchlorhydria, peptic ulcer, diarrhea, dysentery, etc. As an *antidiarrheic*, etc., administer 1 gram of the powder in cocoa or milk. *Externally* it is employed as a powder or in ointments in the treatment of ulcers, burns, eczema and other skin conditions. When used as a prophylactic against *sunburn* spread on as a paste or powder.

Large doses of bismuth subcarbonate—not subnitrate—are used with other agents in the treatment of amebiasis.

In the treatment of gastritis:

℞

Bismuth Subcarbonate	20.0 Gm. (3v)
Sodium Bicarbonate	10.0 Gm. (3iiss)

M. Make 20 capsules.

Sig.: One three times a day before meals.

Bismuth Subnitrate

Bismuth Subnitrate is a basic, nearly insoluble salt, yielding about 79 per cent Bi_2O_3. Its action and uses are very similar to those of bismuth subcarbonate. It yields CO_2 when administered with soluble carbonates and bicarbonates. The internal use of relatively large amounts of the subnitrate for x-ray diagnosis or other purposes may cause toxic manifestations, such as cyanosis, diarrhea, dyspnea, and death by arrest of respiration. The effects are caused by the production of nitrites by the reducing action of putrefactive bacteria in the large intestine.

Titanium Oxide

Titanium, a hard gray-colored metal, is widely distributed in nature. In the United States it is mined in Virginia, Florida, and California.

Titanium oxide (TiO_2) and zinc oxide possess certain properties in common: they are nontoxic, protective, mildly antiseptic, and slightly antacid. They both possess considerable ability to cover surfaces, titanium oxide giving three times the "coverage" for equal bulk. Although the evidence available is somewhat meager, it may be concluded that titanium oxide is about equivalent to zinc oxide in therapeutic value.

Dusting Powders

Dusting powders are dry, fine, insoluble, nonirritating powders, such as talcum, lycopodium, chalk, and starch. They are used for application to irritated, abraded, or inflamed surfaces of the skin or mucous membrane. Their favorable action is due to their protective action against air and from contact with clothes, and also to their absorption of secretions, thus rendering bacterial action less probable. Some of them are antiseptic in character and are used as surgical dressings. Others are popular as toilet accessories and cosmetics. Most of their virtues are due to their mechanical properties rather than to their bactericidal action. Among the agents used for these purposes are starch, calcium carbonate (chalk), magnesium carbonate and oxide, magnesium silicate (talcum), aluminum silicate (kaolin), lycopodium, zinc oxide, titanium oxide, etc.

Talcum is purified, native, hydrous magnesium silicate sometimes containing a small amount of aluminum silicate. It is used as an absorbent and protective and as a diluent for more active agents in the treatment of many moist skin affections, and for cosmetic purposes. *Lycopodium*, the spores of club moss, is sometimes employed as a dusting powder for abrasions, ulcers, etc. Its most common use is to prevent uncoated pills from sticking together. *Prepared Chalk* ($CaCO_3$) is an insoluble, amorphous, tasteless powder used occasionally as a dusting powder but usually internally as an antacid. *Starch* is employed as a protective and diluent, being prescribed with other agents in the form of dusting powders and ointments, in the treatment of prickly heat, intertrigo, dermatitis, and various other skin conditions.

For dusting powder:

℞

Boric Acid	12.00 Gm.	(3iij)
Talc		
Zinc Stearate āā	q.s. ad 120.00 Gm.	(℥iv)

M.

Sig.: Dust on affected area.

Calamine

Calamine is a mixture of zinc oxide and a small amount of ferric oxide. It has a pinkish color and earthy appearance and is odorless and insoluble in water.

It possesses astringent and protective action. It is commonly used in a liniment and lotion in the treatment of skin diseases, such as erythema, dermatitis, eczema, and many similar conditions. One per cent phenol is often added to the lotion. It is occasionally used in ointment form.

For treatment of herpes progenitalis:

℞

Zinc Oxide	1.00 Gm.	(gr.xv)
Calamine	1.00 Gm.	(gr.xv)
Glycerin	2.00 cc.	(f3ss)
Alcohol	2.00 cc.	(f3ss)
Water q.s. ad	60.00 cc.	(f℥ij)

M. Sig.: Apply freely. SHAKE LABEL.

Calamine lotion is widely used to relieve itching. If this is to be used on unbroken skin, equal parts of limewater and rose water make

it less liable to cake and somewhat less drying. If the skin is very dry, glycerin may be added or calamine liniment may be used.

For generalized pruritus Pusey's Calamine Liniment:

℞

Tragacanth powder		4.0 Gm.	(3j)
Phenol			
Glycerin	āā	0.67 cc.	(ℳx)
Calamine			
Zinc oxide	āā	30.00 Gm.	(℥j)
Olive oil		120.00 cc.	(℥iv)
Bergamot Oil		2.00 cc.	(3ss)
Distilled water	q.s. ad.	480.00 cc.	(℥xvj)

M. Sig.: Apply to skin as directed.

PREPARATIONS

Collodion, *Collodium*, U.S.P.

Flexible Collodion, *Collodium Flexile*, U.S.P., B.P.

Bismuth Subcarbonate, *Bismuthi Subcarbonas*, U.S.P. *Bismuthi Carbonas*, B.P. *Dosage:* 1 Gm. (15 grains).

Bismuth Subnitrate, *Bismuthi Subnitras*, N.F. *Dosage:* 1 Gm. (15 grains).

Talc, *Talcum*, U.S.P.

Titanium Dioxide, *Titanii Dioxidum*, N.F.

Lycopodium, *Lycopodium*, N.F.

Calamine Liniment, *Linimentum Calaminae*, N.F. Prepared calamine (8%) and zinc oxide (8%) in an emulsion of olive oil and solution of calcium hydroxide.

Calamine Lotion, *Lotio Calaminae*, U.S.P. Prepared calamine (8%), zinc oxide (8%), and glycerin (2%) and bentonite magma (40%) in calcium hydroxide solution.

IRRITANTS

Irritants are drugs which act locally on cutaneous tissue to produce the typical phenomena of inflammation, "irritation." They injure the protoplasm through coagulation, liquefaction, and other means. They are drugs which injure the skin and thus set up defense mechanisms which operate to protect the tissue. The milder irritants destroy superficial cells, especially if diseased; but the deeper cells multiply more rapidly, facilitating healing and repair. In many skin diseases, irritant or stimulant action is desirable, e.g., chrysarobin in psoriasis.

RUBEFACTION. Drugs which produce a first degree irritation characterized by hyperemia of the blood vessels are called *rubefacients*. The action at first is on the superficial vessels, but penetrates to the deeper structures producing both direct and reflex action. Associated with the hyperemia there is a feeling of warmth, itching, and even pain. If the action is stronger than rubefaction, it may produce vesication or pustulation. Mustard, turpentine, camphor, ammonia, and volatile oils are typical rubefacients. Hot water produces rubefacient action.

VESICANTS are drugs which are capable of producing a greater degree of irritation. They cause the capillaries to dilate widely and become permeable. Plasma escapes into the extracellular spaces, and fluid collects under the epidermis in small and discrete blisters which later coalesce. No fine line of demarcation separates the rubefacients and vesicants, the degree of irritation depending to a large extent on the concentration of the drug and the time during which it is allowed to act. Cantharides and ammonia are typical vesicant drugs.

PUSTULANTS are another type of irritant which do not penetrate the epidermis but only the orifices of the sebaceous glands, acting locally at these sites rather than diffusely over the surface of the skin. Pustulants may produce small multiple abscesses which if the action continues may coalesce. The principal pustulants are croton oil and tartar emetic. *This group of drugs has few therapeutic indications.*

Counterirritation.—Irritants produce (1) local changes (as described above under rubefacients, vesicants and pustulants) and (2) secondary changes (counterirritation).

Secondary changes, or counterirritation, are more general in nature and affect the whole organism. They arise (1) from *reflex stimulation of centers in the medulla oblongata,* and (2) from *vasodilatation in the distant organs* due to reflex stimulation through the posterior roots.

REFLEX STIMULATION IN MEDULLA OBLONGATA.—The medullary centers involved are those regulating the heart, tone of the vessels, and respiration. Temperature, leucocytes, metabolism, and general well-being seem to be affected to some extent by skin irritation. Moderate irritation of the skin accelerates heart rate and increases blood pressure due to reflex stimulation of the vasomotor center, which constricts chiefly the splanchnic vessels, while exaggerated irritation slows the heart and lowers the blood pressure. Moderate irritation results in a greater supply of blood to muscles and skin, and less to the internal organs.

Skin irritants on man cause gasping and irregular respiration. Temperature falls slightly; as a rule internal temperature falls, and skin temperature rises. Metabolism is increased slightly and leucocytosis is evident. Skin irritation seems to have the general effect of awakening the person and improving his mental condition as a whole.

VASODILATATION IN DISTANT ORGANS.—Skin irritants are most frequently employed to influence organs far removed. Many theories have been suggested to explain the effects of counterirritation, but no satisfactory explanation has appeared to satisfy the modern scientific mind.

MECHANISM OF COUNTERIRRITATION.—The afferent nerve fibers from the skin contact in the cerebrospinal axis with efferent vasomotor fibers to internal organs. Thus the increased circulation of the skin produces a similar condition in deeper skin structures and in visceral organs innervated from the same level of the nervous system. Thus when pain arises from an internal organ it is believed that sensory impulses simultaneously coming from the skin as a result of the action of an irritant may either alter the character of the pain or, more likely, occupy the final common pathway to the partial or complete exclusion of pain impulses arising from the viscera.

At the present time physical means are more widely employed for producing hyperemia, irritation, and counterirritation. Heat is often the rubefacient of choice. The hot pack, short wave diathermy, and other common methods of applying heat are used for producing localized hyperemia. Localized circulatory changes may also be produced by parasympathomimetic drugs employed by iontophoresis for the purpose of increasing the blood flow in a localized area.

The relief of pain may be explained partly by diversion of the attention of the patient from disease by the irritants applied, and partly by the explanation based on homologous reflexes.

Therapeutic Uses of Irritants.—Irritant drugs are especially useful in medicine for their reflex stimulant action of the central nervous system and for their stimulant action in certain skin diseases.

Due to the development of more efficient therapeutic agents such as antitoxins, antisera, etc., their use in certain diseases such as

pneumonia, tuberculosis, arthritis, etc., is almost obsolete. Heat lamps and hot packs are usually favored over irritants to produce hyperemia or relieve pain in the treatment of certain conditions.

Many drugs produce irritation and counterirritation. The following are worthy of consideration.

Ammonia

Ammonia, NH_3, is an irritating gas, soluble in alcohol, and in water, in which a part is converted into NH_4OH. Its solutions are incompatible with acids (neutralization), soluble metallic salts (forms hydroxides), and with alkaloidal salts (frees alkaloid). The carbonate on exposure to air frees NH_3, and in aqueous solution, especially hot water, rapidly eliminates NH_3.

Action and Uses.—Ammonia is a stimulant, irritant, and carminative.

Mode of Action.—When inhaled or given internally in therapeutic doses, the irritation of the vapors causes reflex stimulation of the vasomotor centers, with contraction of the arterioles and increased blood pressure. The heart may be temporarily slowed then sped up from reflex action on the vagus, the cardiac muscle, and the vasomotor centers. The action is usually transient, which makes it a valuable agent in sudden collapse, fainting, etc. There also results reflex stimulation of the respiratory center resulting in stoppage, and then deeper and fuller respirations.

Aromatic Ammonia Spirits or Ammonia Water may be inhaled or given internally; place 2 cc. of aromatic ammonia spirits on a handkerchief and inhale fumes, or take orally 2 cc. well diluted. The aromatic spirit has been used as an antacid and carminative. There is some doubt as to its effectiveness. Stronger Water of Ammonia should not be used internally and should be cautiously used only by inhalation. The carbonate is often used either in the form of smelling salts or given orally. Smelling salts usually consist of ammonium carbonate, ammonium chloride, and various volatile oils.

Externally, ammonia is rubefacient; it is used chiefly in the form of liniments. Applied in concentrated form it may blister.

Preparations

Diluted Ammonia Solution, *Liquor Ammoniae Dilutus*, U.S.P., B.P., NH_3 (about (9.5%) in distilled water. *Dosage:* 1 cc. diluted with water.

Strong Ammonia Solution, *Liquor Ammoniae Fortis*, U.S.P. It is an aqueous solution of ammonia containing about 28 per cent of NH_3.

Aromatic Ammonia Spirit, *Spiritus Ammoniae Aromaticus*, U.S.P., B.P. Ammonium carbonate (3.4%), ammonia water (9%) and oils of lemon, lavender, and myristica in alcohol and distilled water. Absolute alcohol content about 65 per cent by volume. *Dosage:* 2 cc. (30 minims).

Ammonia Liniment, *Linimentum Ammoniae*, N.F. Diluted ammonia solution (25%) in oleic acid and sesame oil.

Ammonium Carbonate, *Ammonii Carbonas*, U.S.P., B.P. A mixture of ammonium acid carbonate and ammonium carbamate, yielding about 31 per cent of NH_3. *Dosage:* 0.3 Gm. (5 grains).

Mustard

Sinapis Nigra (black mustard) has been used since the earliest time both in medicine and as a condiment. Now it is used for its emetic,

rubefacient, and vesicant action. The volatile oil is developed from black mustard on contact with water. This volatile oil is the active principle which imparts the pungent odor and taste and the irritant properties to mustard. Black mustard and white mustard are the dried seeds of *Brassica nigra* and *Sinapis alba*, respectively. They are herbs extensively cultivated in Europe and in America. The seeds of both are usually mixed together and supplied as powdered or ground mustard. Black mustard contains a ferment, myrosin, and a glucoside, sinigrin, which decomposes in presence of water as follows:

$C_{10}H_{18}KNS_2O_{10}$	$\rightarrow$	$CSNC_3H_5$	+	$C_6H_{12}O_6$	+	$KHSO_4$
sinigrin		allyl-isosulfocyanate		glucose		potassium bisulfate

Since the irritant action depends upon this fermentation taking place, mustard must not be mixed with very hot water.

Action and Uses.—Mustard is characterized by its emetic, rubefacient, and vesicant action. As an *emetic* a tablespoonful of powdered mustard is given in a glass of warm water. It is used in the form of poultices and plasters in the treatment of *bronchitis, pneumonia,* and as a *counterirritant* in certain neuralgic or rheumatic conditions. As a counterirritant use: 8 tablespoonfuls of flour, 4 tablespoonfuls of mustard, the white of 1 egg, warm water to make a paste; spread on a cloth and apply until redness is produced. It should be used only to produce rubefaction, and ought to be removed before vesication occurs. A mustard plaster should be left on for about ten to twenty minutes. The volatile oil of mustard may be dissolved in alcohol or fixed oils and used as a counterirritant.

PREPARATIONS

Black Mustard, *Sinapis Nigra*, U.S.P. *Dosage:* Emetic 10 Gm. (2½ drachms).

Allyl Isothiocyanate, *Allylis Isothiocyanas*, N.F. Volatile Oil of Mustard. Contains not less than 93 per cent of C_3H_5NCS.

Mustard Plaster, *Emplastrum Sinapis*, U.S.P. A mixture of black mustard, derived from its fixed oil, and a solution of a suitable adhesive, spread on paper, cotton cloth, or other fabric. NOTE: Before applying mustard plaster it should be thoroughly moistened with tepid water (U.S.P.).

Camphor

Camphor, $C_{10}H_{16}O$, is a stearopten or ketone obtained from the volatile oil of Cinnamomum Camphora, the camphor tree of eastern Asia. Camphor may be produced synthetically. It forms white, crystalline masses of characteristic odor and taste. These masses are almost insoluble in water, but are freely soluble in alcohol, ether, chloroform, fixed and volatile oils. Dry camphor volatilizes readily, but its solutions are stable.

Action and Uses.—Camphor is a stimulant, carminative, and antiseptic. On the skin and mucous membranes, camphor is mildly irritant, producing redness and a feeling of warmth and analgesia. ***Externally***, it is applied as a mild analgesic and counterirritant in neuralgia and rheumatism in the form of *Camphor Liniment* (Camphorated Oil), or as Camphor Spirit. It is slightly antiseptic. It is used in "moth balls" as a protection against moths.

Inhaled, administered ***internally*** by mouth, or injected ***hypodermically***, it is used as a cardiac or respiratory stimulant in cases of fainting,

collapse, and anesthetic narcosis. In faintness, weakness, or syncope, it may be inhaled in the form of Camphor Spirit; or this preparation may be given internally in doses of 1 cc. (15 minims) for the same purpose. Hypodermic injections of 1 to 2 cc. of a 10 per cent solution of *camphor in olive oil* or almond oil, repeated in 10 to 15 minute intervals, if necessary, are claimed to be valuable circulatory and respiratory stimulants in collapse from anesthetics and other narcotics. Camphor and the monobromated camphor are used in the treatment of colds, bronchitis, headache, hysteria, and in analgesic and antispasmodic remedies.

As an inhalation for colds:

℞

Camphor
Menthol ..... āā 2.00 Gm. (3ss)
Compound Benzoin Tincture q.s. ad 30.00 cc. (f℥j)
M. Sig.: Use teaspoonful in pitcher of hot water as required.

The systemic effects of camphor are seriously questioned. Straub well expresses this: "In Germany, at least, there was a time when nobody was allowed to die without Camphor."

PREPARATIONS

Camphor, *Camphora*, U.S.P., B.P. *Dosage:* 0.2 Gm. (3 grains).
Camphor Liniment, *Linimentum Camphorae*, U.S.P., B.P. Camphor (20%) in cottonseed oil.
Camphor Water, *Aqua Camphorae*, U.S.P., B.P. *Dosage:* 10 cc. (2½ fluidrachms).
Camphor Spirit, *Spiritus Camphorae*, U.S.P. Camphor (10%), in alcohol. *Dosage:* 1 cc. (15 minims). B.P. 0.3-2 mils. (5-30 mins.).
Monobromated Camphor, *Camphora Monobromata*, N.F. ($C_{10}H_{15}O$ Br). *Dosage:* 0.125 Gm. (2 grains).

Cantharides

Cantharis consists of the dried insects *Cantharis vesicatoria*, and yields not less than 6 per cent cantharidin ($C_{10}H_{12}O_4$). The name "Spanish Flies" given this substance is correct according to Solis-Cohen, except that it is not a fly, and its use did not originate in Spain. The insect is closely related to the "potato bug." Cantharides preparations have been used medicinally since the earliest times but now they are seldom prescribed.

Pharmacological Action.—Cantharides when applied to the skin produce redness, pain, and soon small vesicles which coalesce to large blisters. The action is slow, and penetration is slow, without involvement of the deeper layers. Blisters heal readily, leaving no scars. Application of 0.04 per cent cantharidin produces a blister within half an hour, but cantharides plaster (0.033 per cent cantharidin) requires four to six hours to produce a blister.

When taken internally, cantharidin irritates the alimentary tract, kidney, and urinary passages. When taken orally, the solution blisters the mouth and throat and hinders swallowing. The action on the stomach is severe, causing vomiting and severe pain, often followed by collapse.

Toxicology.—Cantharidin may be absorbed from the intestine, or even from the blisters, and affects chiefly the organs of elimination.

Small quantities irritate the bladder, causing a desire to micturate. Large quantities may cause nephritis and hematuria, and inflammation of the genitourinary tract, producing pain, irritation, priapism, and libido.

Toxic symptoms may be produced by 0.5 gram or less. Death may follow the ingestion of 1.5 to 3.0 grams; it may occur suddenly from shock or be delayed several days and be due to nephritis. Treatment consists of emptying the stomach by lavage or apomorphine. Demulcent drinks and opiates are indicated.

At present cantharidin is contraindicated for use as a diuretic because of its injury to the kidneys and because other diuretics are more effective.

Therapeutic Uses.—Cantharis is sometimes used as a *counterirritant* in the treatment of such conditions as neuralgia and sciatica. It is used in various hair preparations to prevent *alopecia.*

The cerate or plaster is sometimes used for external application. The tincture is used with various other applications in hair preparations. *The drug should never be used internally.*

PREPARATIONS

Cantharides, *Cantharis*, N.F. *Cantharidinum*, B.P.

Cantharides Cerate, *Ceratum Cantharidis*, N.F. Cantharides (35%) with oil of turpentine, glacial acetic acid, yellow wax, rosin, and benzoinated lard.

Cantharides Tincture, *Tinctura Cantharidis*, N.F., B.P. Cantharides (10%), in glacial acetic acid and alcohol. *Dosage:* 0.1 cc. (1½ minims). Its internal use is not desirable.

Chloroform

Chloroform is a heavy, colorless, volatile liquid with a characteristic, penetrating odor and sweetish taste. It is soluble in 200 parts water, freely miscible in alcohol, ether, petroleum, and in fixed and volatile oils. To prevent deterioration keep in amber-colored glass bottles stored in a cool dark place.

Action and Uses.—Chloroform is a general anesthetic, sedative, rubefacient, carminative, anodyne, and antispasmodic. (For general action and toxicology, see Chapter X.) On the skin chloroform may produce redness and even vesication, if evaporation is retarded. It acts as a carminative and intestinal stimulant when given internally. Externally it is an ingredient of liniments used for sprains, strains, etc. Decided rubefacient action is effected by covering the area after applying. The official Chloroform Liniment (chloroform 30% and soap liniment) is used alone or with other agents, or chloroform is prescribed with soap liniment in other preparations.

For external application:

℞

Menthol	4.00 Gm.	(3j)
Chloroform	30.00 cc.	(f℥j)
Camphor and Soap Liniment	180.00 cc.	(f℥vj)

M. Sig.: Apply as directed.

PREPARATION

Chloroform Liniment, *Linimentum Chloroformi*, U.S.P., B.P. A mixture of chloroform (30%), camphor and soap liniment. ***Caution: Chloroform liniment deteriorates with age.***

Turpentine

Turpentine is an oleoresin obtained from various species of *Pinus*. Turpentine and its related preparations have been used since ancient times.

Action and Uses.—Turpentine and its preparations possess an antiseptic, carminative, rubefacient, counterirritant, diuretic, and anthelmintic action. It is readily absorbed from the skin, lungs and intestinal tract. It is excreted largely by the kidneys. Small doses cause noticeable systemic effects. In larger doses (15 to 150 cc.), fatal poisoning may occur.

Since oil of turpentine is very irritating it should be administered as an emulsion or with a bland oil. It is frequently administered as "turpentine stupes." It may be used as a liniment or as a stupe in the treatment of *neuralgia, neuritis,* and *rheumatism.* The "stupe," prepared by adding the oil to flannel cloth, previously soaked in hot water and wrung out, has been a common household remedy for treatment of various rheumatic pains, renal colic, intestinal distention, etc. It must be removed as soon as it produces pain, because otherwise it will blister. The oil is very penetrating, and if vesication is produced the lesions are very painful and heal slowly.

Preparations

Turpentine Oil, *Oleum Terebinthinae*, U.S.P. "Spirits of Turpentine."

Rectified Turpentine Oil, *Oleum Terebinthinae Rectificatum*, N.F. Redistilled turpentine oil. Oleum Terebinthinae, B.P. *Dosage:* 0.3 cc. (5 minims).

Turpentine Oil Emulsion, *Emulsum Olei Terebinthinae*, N.F. Rectified turpentine oil (15%) with acacia and distilled water. *Dosage:* 2 cc. (30 minims).

Turpentine Liniment, *Linimentum Terebinthinae*, N.F., B.P. Rosin cerate (65%) in turpentine oil.

Balsams

Balsams are mixtures of resins, volatile oils, benzoic and cinnamic acids, and their esters. The oils act as antiseptics. The oils and resins are mildly irritant, thus stimulating repair. The resins also furnish local protection, thus aiding healing.

Peruvian Balsam.—This compound, obtained from a tree of Central America, the *Toluifera Pereirae,* contains from 25 to 30 per cent resin and from 55 to 65 per cent of volatile oil (esters of benzoic and cinnamic acids) to which it owes its therapeutic virtues. It is a thick brown liquid, possessing a vanilla-like odor and a bitter taste. It is soluble in alcohol and nearly insoluble in water.

Action and Uses.—Peruvian Balsam is antiseptic, mildly irritant and stimulant to the skin and mucous surfaces. Equal parts of Peruvian Balsam and castor oil are recommended for the treatment of *bed sores.* It is useful in the treatment of *ringworm* (epidermophytosis). The following prescription is useful:

℞

Ether	2.00 cc.	(f℥ss)
Peruvian Balsam	4.00 Gm.	(℥j)
Flexible Collodion q.s. ad	30.00 cc.	(f℥j)

M. Sig.: Open vesicles and apply antiseptically.

Peruvian Balsam, applied as a 10 per cent ointment, is indicated in the treatment of *impetigo contagiosa.* A 4 to 8 per cent concentration in 10 per cent sulfur ointment is indicated in the treatment of *scabies. Internally,* it may be used as a stimulant and disinfectant expectorant in *chronic bronchitis* and other discharges from the mucous membranes. It is said to increase cell division.

TOLU BALSAM.—Like Peruvian Balsam, Tolu balsam is a mixture of resinous matter (75 to 80 per cent) with cinnamic and benzoic acids and their esters. It is a feeble stimulant *expectorant;* Tolu Balsam Syrup has an agreeable vanilla-like flavor. It is insoluble in water, soluble in alcohol. It is an ingredient of Compound Benzoin Tincture, U.S.P., which is often employed in obstinate *catarrhs* by inhalation of the vapor.

As a constituent of cough remedies:

℞

Codeine Sulfate	0.16 Gm.	(gr. iiss)
Sodium Citrate	8.00 Gm.	(℥ij)
Tolu Balsam Tincture	30.00 cc.	(f℥j)
Distilled Water q.s. ad	90.00 cc.	(f℥iij)

M. Sig.: Teaspoonful every two hours.

BENZOIN.—Benzoin is a balsamic resin of *Styrax benzoin,* a tree of South Asia. It has the stimulant and expectorant properties of benzoic acid, and is used for the same purposes. Benzoin contains benzoic acid, cinnamic acid, and resins.

Action and Uses.—Benzoin is useful in the treatment of ulcers, bed sores, and various skin lesions. *Compound Benzoin Tincture* acts as a stimulating expectorant. It is applied as "varnish" to "chaps" or abrasions, ulcerated surfaces, chafed palms, etc. It is mildly antiseptic and astringent. It is frequently administered by adding a teaspoonful to a glass of water and inhaling the vapor. It possesses a pleasant odor and acid taste. Its active constituents are soluble in alcohol and insoluble in water.

As an inhalant in whooping cough:

℞

Menthol Camphor āā	4.00 Gm.	(5j)
Compound Benzoin Tincture q.s. ad	60.00 cc.	(f℥ij)

M. Sig.: Use a teaspoonful in a quart of hot water by inhalation.

PREPARATIONS

Peruvian Balsam, *Balsamum Peruvianum,* U.S.P., B.P. (Peru Balsam.)

Tolu Balsam, *Balsamum Tolutanum,* U.S.P., B.P. (Tolu.)

Tolu Balsam Syrup, *Syrupus Balsami Tolutani,* U.S.P. (Syrup of Tolu). Tolu balsam tincture (5%) with magnesium carbonate, sucrose and distilled water. *Dosage:* 10 cc. (2½ fluidrachms).

Tolu Balsam Tincture, *Tinctura Balsami Tolutani,* U.S.P. Tolu balsam (20%) in alcohol. *Dosage:* 2 cc. (30 minims).

Benzoin, *Benzoinum,* U.S.P., B.P.

Benzoin Tincture, *Tinctura Benzoini,* U.S.P. Benzoin (20%) in alcohol. Absolute alcohol content about 79 per cent. *Dosage:* 1 cc. (15 minims).

Compound Benzoin Tincture, *Tinctura Benzoini Composita*, U.S.P., B.P. Benzoin (10%), aloe (2%), storax (8%), Tolu balsam (4%), in alcohol. Absolute alcohol content about 77 per cent. *Dosage:* 2 cc. (30 minims).

Chrysarobin

Chrysarobin is a mixture of neutral principles obtained from Goa powder, a substance deposited in the wood of a Brazilian tree *Vouacapoua* (Aguiar) *araroba*. It is a brownish material very slightly soluble in water and slightly soluble in alcohol. It is soluble in chloroform (1:23).

Pharmacological Action.—This compound is antiseptic and has a powerful irritant action on the skin. Various hydrocarbons, including coal tar, pyrogallol, resorcin, and chrysarobin, are used to reduce scaling and hypertrophy of the horny layer of skin. Chrysarobin is more active than tar and must be used with caution. It absorbs oxygen readily and is converted into chrysophanic acid. It is strongly irritant to the skin and mucous membranes.

Toxicology.—Chrysarobin when applied to the skin in susceptible persons causes itching, swelling, and pustular eruptions. It should not be used about the eyes. When swallowed it irritates the gastrointestinal tract, causing vomiting and purging. It may injure the kidneys, causing nephritis. Small doses may cause nephritis and albuminuria.

Therapeutic Uses.—*Skin Diseases.*—Chrysarobin is employed as an ointment (5 to 25 per cent) in the treatment of psoriasis, lupus, ringworm, etc. It is also effective against herpes tonsurans, eczema and pityriasis versicolor. It should be applied only over small areas, and should not be allowed to come in contact with the eyes.

In *psoriasis*, chrysarobin is undoubtedly effective in more cases than any other drug. Treatment is usually begun with 5 per cent strength and increased to 25 per cent. The drug may be applied in collodion to be painted on, a method more acceptable to the fastidious patient but less effective than the ointment.

Chrysarobin is a potent drug and should not be employed on the scalp or face because of the danger of setting up a severe dermatitis.

For psoriasis (Sutton and Sutton):

℞

Chrysarobin ---------- 4.0 Gm. (3j)
Petrolatum ----------q.s. 30.0 Gm. (℥j)
M. Sig.: Rub in three times daily. (The activity of this irritant is promptly counteracted by the application of 1:3000 aqueous solution of potassium permanganate.)

Dioxyanthranol is a synthetic compound resembling chrysarobin. It is said to be more active, less toxic, and more pleasant to use than chrysarobin.

Preparations

Chrysarobin, *Chrysarobinum*, U.S.P., B.P.
Chrysarobin Ointment, *Unguentum Chrysarobini*, U.S.P. (6%), B.P. (4%). Chrysarobin (6%), yellow ointment (87%), and chloroform (7%).

Juniper Tar

Juniper tar (oil of cade)' is a dark brown, thick liquid having a tarry odor and an aromatic bitter taste. It is slightly soluble in water and partially soluble in alcohol. It is a volatile oil.

Action and Uses.—Juniper tar possesses antiseptic, irritant, and expectorant action. It is used as an epidermal stimulant in chronic inflammatory diseases; it acts like tar. It is usually prescribed with other agents and is well diluted with a bland ointment base.

In the *chronic stage of eczema* the best available preparations are cade oil and pine tar. Juniper tar may be the least unpleasant. In the treatment of *scabies* 10 per cent juniper tar is added for antipruritic effect in the following prescription.

℞

Juniper Tar	12.00 cc.	(f℥iij)
Sulfur	24.00 Gm.	(℥vj)
Soft Soap	30.00 cc.	(f℥j)
Petrolatum	48.00 cc.	(f℥iss)

M. Sig.: Apply externally as directed.

Preparation

Juniper Tar, *Pix Juniperi*, U.S.P.

Pine Tar

Pine tar is a product obtained by the destructive distillation of the wood of various species of pines *(Pinus)*. It is a black semiliquid material with an empyreumatic odor and taste. It is soluble in alcohol, but only slightly soluble in water. When tar is distilled it yields a liquid portion, rectified oil of tar (used as an external antiseptic, irritant, parasiticide, and in skin diseases), acetic acid, and black rosin-like residue. The composition of pine tar is largely phenolic and upon this depends its medicinal value.

Action and Uses.—Its most important internal use is as a stimulating *expectorant* for chronic bronchitis. It is used externally as a stimulating and antiseptic application for *chronic skin diseases*, such as eczema, psoriasis, tinea, and scabies. Its anesthetic properties make it valuable as an *antipruritic*.

Pine tar may be prescribed with other agents, such as phenol, boric acid, sulfur, etc., and well diluted with a bland ointment base. Pine Tar Ointment is antipsoriatic, antiseptic, astringent, and is said to promote healing in chronic skin lesions.

In treatment of chronic eczema:

℞

Pine Tar	2.00 Gm.	(3ss)
Precipitated Sulfur	2.00 Gm.	(3ss)
Zinc Oxide Ointment q.s. ad	30.00 Gm.	(℥j)

M. Sig.: Apply as directed.

All tars are stimulating and must be used with caution in dermatitis. It is a good plan to try out the tar preparation on a small part of the inflamed area before applying it to a larger area. If continued too long, tars often cause folliculitis, and they must be discontinued.

For infantile eczema (Tuft's Clinical Allergy).

℞

Pine Tar	8 Gm. (3ij)
Zinc Oxide	16 Gm. (3iv)
Starch	30 Gm. (3j)
Petrolatum	120 Gm. (3iv)

Mix and make an ointment.

Sig.: Apply as directed. (If it causes irritation, use only one drachm of coal tar in mixture.)

When applied in a thin coat this ointment is antipruritic, drying, and very effective in infantile eczema. The ointment should be renewed at least once a day, after removal with oil. If more body to the ointment is desired, the amount of zinc oxide may be increased.

PREPARATIONS

Pine Tar, *Pix Pini*, U.S.P. Pix Liquida, B.P.
Rectified Tar Oil, *Oleum Picis Rectificatum*, U.S.P., B.P.
Pine Tar Ointment, *Unguentum Picis Pini*, U.S.P. Pine tar (50%), yellow wax (15%) and yellow ointment (35%)

ASTRINGENTS

Astringents are substances which, acting locally, produce visible contraction of tissue, blanching and wrinkling of mucous membranes, and diminished exudation. On local application to the skin or mucous membrane they produce a slight precipitation of the proteins on the surface layers of the tissues; this leads to a slight shrinkage of these layers, with a loss of some of their sensitivity, especially if an inflammatory condition exists. In the mouth and throat astringents produce a puckering sensation.

When applied to inflamed mucous membranes or to wounds they produce on the surface a thin protective film, diminish formation of transudation of secretions, check migration of leucocytes and the formation of pus, and contract superficial tissues. The precipitation of the superficial protein layers resulting in hardening of the epidermis reduces the absorption of toxins and protects the inflamed mucosa against irritants. Some claim that astringent drugs have a vasoconstrictor action, thus diminishing the size of the vessels, and consequently decreasing the amount of exudation from them. Astringent action may lessen secretion on mucous membranes by direct action on the secretory cells or possibly a better explanation is that the lessened secretion is due to the indirect results of the protection afforded the surface cells.

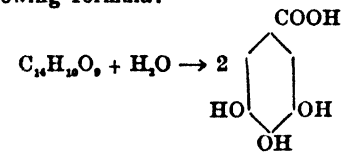
Astringents are used for the following purposes:

1. To protect inflamed mucous surfaces.
2. To reduce hypersecretion.
3. To relieve diarrhea and dysentery.
4. To reduce swelling, inflammation, and secretion in urethritis.
5. To prevent bleeding from small wounds.

The most commonly used astringents are Vegetable Astringents (tannic acid, acetyltannic acid, albumin tannate, krameria, kino) and Metallic Astringents (alum, copper sulfate, zinc sulfate, lead acetate, Monsel's solution).

TANNIC ACID AND DERIVATIVES

Tannic acid, tannin, $HC_{14}H_9O_9$, is usually obtained from young twigs of certain oak trees, and is the result of the puncture and deposited ova of a small insect. It is odorless, bitter in taste, and very soluble in water, alcohol, or glycerin. It is incompatible with most metallic salts, albumin, oxidizers, and alkaloids. The acid commonly referred to as tannic acid is *gallotannic acid*, the anhydride of *gallic acid*. The chemical relationship between gallic acid and tannic acid is expressed in the following formula:



Gallotannic Acid Gallic Acid

Pharmacological Action.—The most important pharmacological action of tannic acid, or the tannins, is its activity as a precipitant. Due to its protein precipitant action it acts as an astringent, hemostatic, and antiseptic, the latter mainly by depriving bacteria of food.

Besides being a protein precipitant, tannic acid also forms insoluble complexes with many heavy metals, alkaloids, and glycosides. This action makes tannic acid an excellent chemical antidote in poisoning.

Tannic acid has little action on intact skin, but on abraded tissue it precipitates protein and acts as a protective due to a film of precipitated proteins.

Many plant preparations of crude drugs contain tannic acid and its precipitant action with proteins, alkaloids, and glycosides must be remembered in compounding prescriptions.

Action on the Gastrointestinal Tract.—When taken orally, some of the tannic acid unites with proteins before it reaches the stomach. Some digestion takes place, forming tannic acid again. The astringent action continues for some time in the intestine by combining with proteins and suppressing mucous secretion. The administration of tannic acid probably has little effect on the peristalsis of the normal intestinal tract, but it does tend to arrest diarrhea by temporarily allaying intestinal inflammation through its astringent action. Tannin may also affect the intestinal flora by precipitating the yeasts and microorganisms. This action would tend to lessen putrefaction and decrease peristalsis, and possibly prevent absorption of toxic products.

Toxicology.—Small doses of tannic acid produce a bitter taste, dryness of the mouth, and partial loss of taste. Nausea, vomiting, and hard stools result. Larger doses produce corrosion, pain, vomiting, and diarrhea or constipation.

Therapeutic Uses.—Internally, tannic acid has been used in the treatment of diarrhea; but tannic acid itself produces excessive gastric irritation. This has prompted the introduction of relatively insoluble tannin compounds which would have little action on the stomach due to insolubility in acid solution, but with greater action in the intestine due to solubility in alkaline solution. This object has not been entirely attained due to the varying pH of the intestinal contents.

Diarrhea.—Internally, tannic acid is seldom prescribed as such; its less soluble derivatives, acetyltannic acid, albumin tannate, and protan, are preferred. As has been explained, acetyltannic acid and albumin

glycerin, and nearly insoluble in alcohol. It is incompatible with alkalies, carbonates, salts of lead, mercury, iron, and tannic acid.

Action and Uses.—Alum possesses astringent, styptic, and emetic action. It is rarely used internally. The Powdered Alum or the Exsiccated Alum may be prescribed alone or with other agents as astringent powders, lotions, or douches.

Solutions of alum are used locally in the treatment of *hyperhidrosis*, to harden skin, and as a vaginal douche in *vaginitis*. Locally, Exsiccated Alum is used to arrest bleeding.

Solution of Aluminum Subacetate is used as a mild irritant, astringent, and antiseptic in *dermatology*. This solution, diluted with 5 to 10 parts of water, is useful in the treatment of eczema in the early stage. Alum and sodium bicarbonate are used in baking powder.

PREPARATIONS

Alum, *Alumen*, U.S.P., B.P. *Dosage:* As a gargle, in from 1 to 5 per cent solution (somewhat injurious to the teeth); as an injection in gonorrhea, in from 0.5 to 1 per cent solution; as a lotion in skin diseases, in 1 per cent solution.

Exsiccated Alum, *Alumen Exsiccatum*, U.S.P. Anhydrous $AlNH_4(SO_4)_2$ or anhydrous $AlK(SO_4)_2$.

Aluminum Acetate Solution, *Liquor Alumini Acetatis*, N.F. Yields about 1.3% Al_2O_3 and about 5% CH_3COOH.

Copper Sulfate.—Copper sulfate in dilute solutions is astringent, while concentrated solutions are caustic. Like other metallic salts, it precipitates proteins, forming albuminates and liberating free acid.

Solutions of 0.1 to 3 per cent may be employed as astringents in *conjunctivitis*, *urethritis*, and *vaginitis*. Its use as a mouthwash or as an oral antiseptic has the disadvantage of producing greenish stains on the teeth. It is used in 1.5 to 2 per cent solutions in the treatment of *ulcerative stomatitis*.

Zinc Sulfate.—Zinc sulfate possesses an astringent action similar to that of copper sulfate, though milder and less irritant. Solutions of 1 to 5 per cent are used as astringent washes in catarrhal and ulcerative *stomatitis* and *pharyngitis*. Solutions of 0.25 to 0.5 per cent are indicated for eyewashes in *conjunctivitis*. Irving recommends zinc sulfate (0.6 Gm. to 30 cc. water) in the treatment of *poison ivy*.

The use of an astringent, such as zinc sulfate, is indicated to overcome the catarrhal condition of the mucous membrane in the terminal stages of *gonorrhea*. Zinc sulfate may be used alone or with phenol, resorcin, or lead acetate. The following is an acceptable prescription.

℞

Zinc Sulfate	0.75 Gm. (gr.xij)
Lead Acetate	1.30 Gm. (gr.xx)
Water q.s. ad	120.00 cc. (℥iv)

M. Sig.: Apply as directed twice daily.

Lead Acetate.—Lead acetate and lead subacetate ("lead water") solutions are more astringent and less irritating than other metallic salts (McGuigan). A saturated alcoholic solution is used as a lotion in Rhus (ivy) poisoning, but its application should not be continued too long. Lead acetate has been employed in the treatment of diarrhea, dysentery, gonorrhea, vaginitis, and various skin diseases; lead solutions, however, are so liable to produce chronic poisoning that they should

never be used internally or on open surfaces; and even on skin diseases their use should be with extreme caution.

Solution of Lead Subacetate, diluted from 15 to 30 times before application, is employed as an astringent and antipruritic in inflammatory conditions of the skin and as an application to bruises. *Caution* should attend its use on denuded surfaces.

Preparations

Cupric Sulfate, *Cupri Sulfas*, U.S.P., B.P. *Dosage:* 0.3 Gm. (5 grains).

Zinc Sulfate, *Zinci Sulfas*, U.S.P., B.P. *Dosage:* Locally, 0.1 to 1 per cent in collyria; 0.5 to 4 per cent in injections (gonorrhea).

Lead Acetate, *Plumbi Acetas*, U.S.P., B.P. Lead acetate (sugar of lead) contains from 85.31 to 89.57 per cent of $Pb(C_2H_3O_2)_2$. Solutions of lead salts are incompatible with carbonates, hydroxides, iodides, chlorides, and sulfates.

Lead Subacetate Solution, *Liquor Plumbi Subacetatis*, N.F. Contains lead subacetate corresponding to about 22% lead. Liquor Plumbi Subacetatis Dilutis, B.P.

STYPTICS

Styptics are remedies used to check hemorrhage when applied locally. The most common are sodium alum, silver nitrate stick, solutions of ferric chloride, ferric subsulfate (Monsel's solution), epinephrine solution, thromboplastin (5%), and tannic acid. Antipyrine, local anesthetics, cotarnine salts, Dakin's solution, and peptone increase bleeding.

CAUSTICS OR CORROSIVES

Caustics or corrosives are agents which destroy normal and necrotic tissue through their chemical and physio-chemical action. The ancient, and even the modern, practitioner used the red hot iron for *actual cautery*. The *electric cautery* is used for removing small growths, for treatment of indolent ulcers, and for treatment of snake and dog bites.

Caustic drugs are closely related to irritants, antiseptics, and astringents. In fact the chief differences that lie between these classes of drugs are due largely to the concentration of drug employed. Many drugs which are caustic in full strength are antiseptic, irritant, and astringent at lesser concentrations. Caustics destroy living and dead tissue, some acting superficially and others penetrating more deeply. Since they destroy organic matter they are also disinfectants.

In the treatment of certain skin diseases, such as lupus vulgaris, warts, etc., actual destruction of the lesions by means of caustics is employed.

Mode of Action of Caustics.—Caustic drugs act in the following ways:

1. By Precipitating Proteins.—Many of the acids and salts of metals are protein precipitants and active caustics. The caustic metallic salts, such as zinc chloride, not only precipitate protein, but also liberate free acids which are irritant and caustic.

2. By Oxidation and Reduction.—Strong oxidizing agents, such as chromic trioxide (chromic acid), arsenic trioxide, and potassium permanganate crystals, liberate oxygen, which chemically unites with hydrogen of the cell molecules of the tissues and thus disintegrates and destroys them.

3. By Hydration.—The concentrated mineral acids and caustic alkalies have an ability to destroy cells by *extracting water* from them. Concentrated sulfuric acid has a powerful ability to split off H + O with carbon, leading to *carbonization* and subsequent death of the tissue cells. Besides carbonizing cells the mineral acids precipitate protein.

The caustic alkalies may saponify fats (form soaps), producing escharotic effects.

4. By Dissolution of Proteins.—Sodium, potassium, and calcium hydroxides are powerful caustic alkalies. Potassium and sodium carbonates are very mild caustic alkalies.

Use of Caustics.—Caustics, corrosives, and escharotics are used for the following purposes: (1) to remove warts, hypertrophies, and other growths; (2) to sterilize bites from dogs, snakes, etc.; (3) to stimulate growth and repair of indolent granulation; (4) to destroy such infections as chancres, carbuncles, etc.; (5) to stimulate healing and repair of fistulas, abscessed tracts, etc.

Toxicology of Caustics and Corrosives.—Poisoning by caustics taken orally is characterized by burning, pain, dysphagia, and loss of tissue. The taste is characteristic of the type of caustic, i.e., acid, alkaline, metallic, etc.

Further symptoms are those of severe gastroenteritis. Bloody vomitus and diarrhea are characteristic findings. Collapse, shock, and rise in temperature may follow from destruction of tissue and absorption of chemical products from injured areas. Perforation may follow extreme caustic action; then the clinical picture resembles that of peritonitis. Death may result from shock, or it may follow in a few days from gradual collapse. Scar tissue followed by gradual stenosis may lead to extremely dangerous after effects. For example, the esophagus may be constricted by scar tissue formation, resulting in starvation unless repeated dilatation is performed to allow for passage of food. *Post-mortem findings* are those of characteristic stains and corrosions of the alimentary tract.

Treatment.—Use vinegar or diluted acetic acid to neutralize alkali poisons, followed later by demulcents such as olive oil to protect irritated mucous membranes. If the poison is a caustic acid, administer magnesia magma, 100 to 500 cc., or if not available, sodium bicarbonate solution or even water to dilute the poison. White of egg or olive oil as a demulcent is indicated. The pain may require the use of morphine. Stimulants may be necessary; if so, administer caffeine hypodermically. If the caustic produces a severe *action on the skin* the treatment is like that for burns, mainly neutralizing and removing the corrosive agent. Salves and oils are useful.

The commonly employed caustics are: chromic trioxide, arsenic trioxide, silver nitrate, nitric acid, acetic acid, trichloroacetic acid, salicylic acid, cupric sulfate, zinc chloride, iodine, and various alkalies.

Chromic Trioxide

Chromic trioxide (CrO_3) is a dark purplish-red, crystalline or needlelike substance. It is deliquescent in air and soluble in water (1:0.6).

Action and Uses.—Chromium trioxide is an active and powerful caustic. It is an oxidizing cauterant difficult to control, hence its usefulness is limited. The pure crystals or solutions of from 25 to 50 per cent strength may be used for destruction of *ulcers, corns, warts,* and other growths. Chromic "acid" is applied to warts in 20 per cent

solution. In 5 to 10 per cent solution it is recommended for local application to the gingivae in *Vincent's infection* and for *ulcerative stomatitis.*

In *nasal hemorrhage* from ulcer of the septum, Holt recommends application of chromium trioxide to the ulcer. Dilute solutions are used to check local sweating.

Arsenic Trioxide

Arsenic trioxide (As_2O_3) is a tasteless, white powder, soluble in water (1:30 to 1:100) and slightly soluble in alcohol. It is readily dissolved in acid or alkaline solutions. Solutions of arsenic are incompatible with salts of iron and of magnesium, limewater, and tannic acid.

Action and Uses.—Locally, arsenic trioxide is a protoplasm poison, producing inflammation and death of tissues. When applied to denuded or ulcerated tissue it has a mildly caustic and painful action. It has been used as a caustic, especially for *malignant growths,* but the painful character of its applications, and danger of absorption have limited its use. Because of its stimulating and beneficial action on skin, characterized by innervation and nutritional disturbances, arsenic is used with considerable benefit in such diseases as *psoriasis, lichen planus, pemphigus,* and *lupus erythematosus.*

In lupus erythematosus equal parts of arsenic trioxide and acacia are made into a paste with a saturated solution of cocaine hydrochloride and spread over the diseased area. Treat only one square inch at a time, leaving on for 24 hours.

Silver Nitrate

Silver nitrate, $AgNO_3$, is a colorless, grayish black crystalline substance, soluble in water (1:0.4) and in alcohol (1:30). It is incompatible with the halides, carbonates, and hydroxides.

Action and Uses.—Silver nitrate acts as an astringent, irritant, or caustic, according to the strength and duration of its application. The skin turns white, gray, and finally black by reduction to metallic silver and oxide. The caustic and astringent action may be stopped by sodium chloride.

Silver nitrate is applied as a mild caustic to wounds, ulcers, and exuberant granulations. As a caustic, it is used in the form of toughened silver nitrate (silver nitrate plus 5% silver chloride). This is moistened and applied on affected areas.

Nitric Acid

Nitric acid is a colorless, fuming, caustic liquid, miscible with water, and containing 68 per cent, by weight, of hydrogen nitrate (HNO_3). It is almost universally incompatible.

Action and Uses.—Nitric acid is a powerful caustic, being used for removing warts and small nevi, for *cauterizing chancroids* and other sores, and for cauterizing dog bites (rabies). In *rabies* cauterize wound at once with fuming nitric acid. When being used for caustic purposes, the surrounding healthy tissue should be protected by a coating of petrolatum and the acid applied with a glass rod or wooden applicator.

In treating *warts* nitric acid is applied full strength with a glass rod and neutralized with salt solution when it has corroded deeply enough.

In cauterizing chancroid ulcers, the ulcer is well cleaned, then wet with a 10 per cent solution of cocaine hydrochloride. After drying, the area is carefully covered with a thin layer of concentrated nitric acid.

In "canker sores" the application of the silver nitrate stick is effective.

Acetic Acid

DILUTE ACETIC ACID is officially prepared by adding 15.8 cc. of acetic acid to enough distilled water to make 100 cc. Good vinegar corresponds approximately to dilute acetic acid. It is used as a local astringent, and internally or by inhalation as a stimulant.

GLACIAL ACETIC ACID is employed as an escharotic. The crystalline form is mainly employed with sulfate of potassium in the preparation of smelling-salts.

TRICHLOROACETIC ACID is prepared by treating acetic acid with chlorine. It occurs in the form of deliquescent crystals and is used as an escharotic for the removal of *warts, corns, small tumors,* and *hypertrophies.* It may be applied to warts with a glass rod. In 5 to 10 per cent solutions it may be applied to *chronic ulcers* and *mucous patches.* Trichloroacetic acid may be used on the lesions of *lupus erythematosus* by painting on with a cotton applicator once a week, the parts having first been cleansed with benzene to facilitate penetration. Scars including those caused by smallpox are reported to be sometimes successfully removed by trichloroacetic acid.

Salicylic Acid

Salicylic acid, $HC_7H_5O_3$, is a colorless crystalline powder, slightly soluble in water (1:460) and freely soluble in alcohol (1:2.7). It is incompatible with iron salts and with spirit of ethyl nitrite.

Action and Uses.—Salicylic acid is antiseptic, stimulant, and somewhat corrosive. When applied to skin salicylic acid, in a concentrated solution, produces a slow painless destruction of epithelium. Strong solutions also cause considerable irritation and superficial corrosion of mucous membranes. Since it softens enamel on teeth, it should not be used in mouthwashes.

Solutions of from 1 to 20 per cent in flexible collodion are used as keratolytic agents in the treatment of *corns.* Salicylic acid in about 20 per cent concentration, combined with various other agents, such as collodion, lanolin, etc., is used in the treatment of *warts.* Because of the keratolytic action of salicylic acid, it is a constituent of many formulas used in the treatment of skin diseases when mild caustic or keratolytic action is desired.

Cupric Sulfate

Cupric sulfate, $CuSO_4.5H_2O$, occurs as large transparent, blue, odorless crystals, granules, or powder, having a nauseous, metallic taste. It is soluble in water (1:3), but only slightly soluble in alcohol (1:500).

Action and Uses.—Cupric sulfate is astringent in small doses and caustic in large doses, depending on the concentration used.

It is employed as a mild caustic in *trachoma.* As a caustic, a crystal or pencil (made by fusing one part of potassium alum and two parts of cupric sulfate) is used. In treating *trachomatous lids* the affected parts of the everted lids are touched lightly with the copper stick and the

eye is then washed with warm water. Cupric sulfate is also used in the treatment of *chancroid ulcers*. The ulcer is first anesthetized with 10 per cent cocaine solution, then a 25 per cent copper sulfate solution is applied. This is left on for three to four minutes, followed by a dusting powder (thymol iodide) or by a gauze spread with petrolatum. In *ringworm* (epidermophytosis) 0.4 per cent copper sulfate may be applied to the vesicles after they are opened aseptically.

Zinc Chloride

Zinc chloride, $ZnCl_2$, is a white granular powder; it may be a mass or be made into pencils. It is very soluble in water or alcohol.

Action and Uses.—Zinc chloride is used as an escharotic on granulations, ulcers, etc. In the treatment of *chancroid ulcers*, the lesion is cleaned with a 10 per cent solution of cocaine hydrochloride, then touched with phenol. The phenol is cleaned off with water and zinc chloride is applied for its caustic action. Its action should be stopped soon after application by flushing with water.

Iodine

Iodine is a heavy, bluish-black, crystalline substance, with a sharp odor and acrid taste. It is slightly soluble in water (1:3,000), but soluble in alcohol (1:12.5) and in solutions of iodides.

Action and Uses.—Iodine irritates the skin, causing a sensation of heat and itching. In concentrated solutions it possesses blistering and caustic action. It penetrates into the deeper layers of the skin, inducing congestion of the underlying layers.

Iodine is often applied as a caustic germicide to *corneal ulcers*. It may be applied cautiously with a toothpick. In *spider bite* there is no rational indication for local treatment of the site of the bite other than the application of tincture of iodine. General discussion, Chapter XXIII.

Various Alkalies

Potassium and sodium hydroxide occur as hard, white, translucent, fused masses, or pencils, with acrid, caustic taste. They are soluble in water and in alcohol.

Action and Uses.—The hydrates of these substances owe their action to the OH ion. Hydroxyl ions are also liberated, but more slowly and in less degree from the carbonates, and still less from the bicarbonates. The hydroxides neutralize acids, dissolve proteins, saponify fats, and dehydrate tissues. Thus they are active caustics, penetrating deeply and causing widespread destruction of tissue; they are difficult to control. The carbonates act similarly but more slowly and less vigorously.

Potassium and sodium hydroxide are powerful caustics. Applied to soft tissues, they produce pain and a slough. Dilute alkalies are used also to soften epidermis and hair, and to emulsify and dissolve fats. They are used in skin diseases to facilitate the penetration of antiseptic remedies into the skin in the treatment of such diseases as scabies, favus, and ringworm.

Toxicology.—The usual symptoms when strong alkalies have been swallowed are burning, difficulty in swallowing, sloughing tissues, vomiting blood and tissues. Later symptoms may include collapse, convulsions, unconsciousness, or coma. *Treatment* consists of giving vinegar or diluted acetic acid to neutralize the alkali. Later, administer demulcents such as

olive oil to protect the irritated membranes. On account of the deep action, stricture of the esophagus is a frequent sequel, and the mortality is high.

Sodium or potassium hydroxide, in 5 per cent strength, is used in dermatology to remove cuticle and keratolytic tissue.

Preparations

Chromium Trioxide, *Chromii Trioxidum*, U.S.P., B.P.
Arsenic Trioxide, *Arseni Trioxidum*, U.S.P., B.P. *Dosage:* 0.002 Gm. ($\frac{1}{30}$ grain).
Nitric Acid, *Acidum Nitricum*, N.F., B.P.
Trichloroacetic Acid, *Acidum Trichloroaceticum*, U.S.P.
Zinc Chloride, *Zinci Chloridum*, N.F.
Potassium Hydroxide, *Potassii Hydroxidum*, U.S.P., B.P. KOH (not less than 85%).

References

Fantus, Bernard: Technic of Medication, Chicago, 1939, American Medical Association.

Goodman, Herman: Cosmetic Dermatology, New York and London, 1936, McGraw-Hill Co.

Lehmann, C. F.: Dermatology in the Army, J. A. M. A. 119: 1469, 1942.

Lyman, R. A.: American Pharmacy, Philadelphia, 1945, J. B. Lippincott Co.

New and Nonofficial Remedies, Chicago, 1947, American Medical Association.

Rosenau, M. J.: Preventive Medicine and Hygiene, ed. 6, New York, 1940, D. Appleton-Century Co.

Sollmann, Torald: A Manual of Pharmacology, Philadelphia, 1948, W. B. Saunders Co.

Sulzberger, M. B., and Wolf, Jack: Dermatologic Therapy in General Practice, Chicago, 1942, Year Book Publishers, Inc.

Sutton, R. L., and Sutton, R. L., Jr.: Synopsis of Diseases of the Skin, St. Louis, 1942, The C. V. Mosby Co.

The Pharmacopoeia and the Physician, Chicago, 1936, American Medical Association.

Tuft, Louis: Clinical Allergy, Philadelphia, 1938, W. B. Saunders Co.

Wise, F., and Wolf, J.: The Pharmacopoeia and the Physician; Use of Dermal Parasiticides, J. A. M. A. 107: 1126-1132, 1936.

Wood, G. B., and LaWall, C. H.: United States Dispensatory, ed. 23, Philadelphia, 1943, J. B. Lippincott Co.

CHAPTER VI

DRUGS ACTING ON SKIN AND MUCOUS MEMBRANES

II. CARMINATIVES, BITTERS, GASTRIC ANTACIDS, DIGESTANTS, EMETICS, EXPECTORANTS, ADSORBENTS, AND CATHARTICS

CARMINATIVES

Carminatives are drugs used to promote the expulsion of gas from the stomach and intestines, and to diminish the "griping" pains without in themselves acting as cathartics. The pharmacological explanation of their mode of action is unsatisfactory. However, practitioners of long experience have considerable faith in their virtues. This group of drugs includes capsicum, cloves, ginger, and volatile oils generally.

Pharmacological Action.—The action of volatile oils upon the isolated stomach or gut is to inhibit activity. Certain pharmacologists believe that they act by relaxing the muscular coats of the stomach and intestines, others are of the opinion that they increase intestinal peristalsis. The injection, however, of these oils into intestinal fistulas in unanesthetized dogs causes an increased peristaltic activity of the gut (Plant and Miller, 1926). Muirhead and Gerald (1916) showed that diluted solutions of volatile oils 1:50,000 caused increased intestinal tone, while concentrations of 1:5,000 caused relaxation. They are usually used in low concentration. Cocaine entirely stops their effectiveness.

Therapeutic Uses.—Turpentine enemas, prepared by adding 20 cc. of turpentine oil to a pint of soapy water, are useful in treating dangerous postoperative tympanites. A few drops of oil of peppermint (5 minims) dropped on a lump of sugar may be used for the treatment of flatulence. The administration of a carminative may prove a valuable supplementary treatment in gallstone colic, dyspepsia, seasickness, etc. The following carminative prescription is satisfactory:

℞

Capsicum Tincture	2.00 cc. (f3ss)
Peppermint Spirit	8.00 cc. (f3ij)
Ginger Fluidextract	10.00 cc. (f3iiss)
Alcohol q. s. ad	120.00 cc. (f3iv)

M. Sig.: One teaspoonful well diluted every half hour as required.

PREPARATIONS

Peppermint Oil, *Oleum Menthae Piperitae,* **U.S.P., B.P.** *Dosage:* 0.1 cc. (1½ minims).
Fennel Oil, *Oleum Foeniculi,* **U.S.P.** *Dosage:* 0.1 cc. (1½ minims).
Anise Oil, *Oleum Anisi,* **U.S.P., B.P.** *Dosage:* 0.1 cc. (1½ minims).

Ginger, *Zingiber*, U.S.P. *Dosage:* 0.6 Gm. (10 grains).

Ginger Fluidextract, *Fluidextractum Zingiberis*, U.S.P. Ginger (100%). Absolute alcohol content about 73 per cent. *Dosage:* 0.6 cc. (10 minims).

BITTERS

Bitters (often called stomachics) are medicines supposed to increase the appetite and improve digestion, and thus favor nutrition. These remedies have always played a prominent role in "folk" medicine. They contain bitter principles, glycosides, aromatics, tannin, etc., on which they depend for their activity. Certain pure alkaloids, such as quinine or strychnine, may be used as bitters.

Mode of Action.—Their method of action has not been demonstrated. The aromatics and condiments may act by mild irritation, with a consequent development of hyperemia and motor stimulation, of the gastric mucosa. All these substances stimulate the taste buds in the mouth and excite the psychic flow of gastric juice.

Modern scientific investigations have shown that bitters may improve deficient appetite and the flow and quality of the gastric juice in conditions of poor health (Moorhead, 1915). They may also exert beneficial antiseptic action.

The commonly used bitters are: Gentian, Tincture of Nux Vomica, and Compound Gentian Tincture.

Therapeutic Uses.—Bitters are used to increase appetite, to improve digestion in all kinds of "atonic" dyspepsias, and to improve the taste of foods and medicines.

They should be administered about ten to fifteen minutes before meals. They are best administered when blended, as in the aromatic and compound bitters, such as Compound Cardamom Tincture and Compound Gentian Tincture. They are, however, often employed in combination with more active agents and compounded in pill or capsule form. Since the element of taste is an important factor in their use, they should not be administered in the form of pills and tablets.

As a bitter tonic:

℞

Nux Vomica Tincture ---------- 15.00 cc. (f℥iv)
Compound Gentian Tincture q.s. ad 120.00 cc. (f℥iv)
M. Sig.: Teaspoonful in water before meals.

Rationale.—Bitters are rarely prescribed in modern medicine. Bitter tonics often regarded by the laity as cures for underweight usually possess an unpleasant taste and often decrease rather than increase the appetite. Their psychic action may be beneficial, however, and they should be prescribed if actually indicated.

PREPARATIONS

Compound Cardamom Tincture, *Tinctura Cardamomi Composita*, U.S.P. Cardamom seed (2%), cinnamon, caraway, and cochineal in diluted alcohol and glycerin. Alcoholic content about 45%. *Dosage:* 4 cc. (1 fluidrachm).

Gentian, *Gentiana*, U.S.P., B.P. *Dosage:* 1 Gm. (15 grains).

Compound Gentian Tincture, *Tinctura Gentianae Composita*, U.S.P., Gentian (10%). Bitter orange peel and cardamom seed in glycerin, alcohol, and distilled water. Alcohol content about 45%. *Dosage:* 4 cc. (1 fluidrachm).

Nux Vomica Tincture, *Tinctura Nucis Vomicae*, N.F. Nux Vomica (10%) yielding about 0.115% strychnine. Alcohol content about 70%. *Dosage:* 1 cc. (15 minims).

Iron Quinine and Strychnine Elixir, *Elixir Ferri, Quininae et Strychninae*, N.F. Ferric citrochloride tincture (12.5%), quinine hydrochloride (0.8%), strychnine sulfate (0.0175%), compound orange spirit, alcohol, glycerin, and water. Alcoholic content about 24.5%. *The elixir should not be dispensed if markedly darkened in color. Dosage:* 4 cc. (1 fluidrachm).

GASTRIC ANTACIDS

Antacids are employed primarily to reduce or neutralize the acidity of gastric secretion, preferably by local action. They are employed clinically chiefly in the treatment of hyperchlorhydria and peptic ulcer, and by the laity in various advertised mixtures for self-medication of any condition which seems to originate in the stomach. Indiscriminate use of antacids by the laity should be discouraged.

The etiology of ulcer is obscure despite the numerous theories which have been set forth. Therapy seeking to counteract or remove the theoretical cause of ulcer (infection, spasm, amino acid deficiency, etc.) is ineffective. Sippy (1915) showed that regardless of the cause of ulcer, constant neutralization of the gastric contents resulted in ulcer healing.

Many other remedies, besides antacids, have been used in peptic ulcer, but they have no particular advantages or are still in the experimental stage. These include gelatin, various vegetable gums, histidine injections, sodium alkyl sulfate to inhibit pepsin activity; antihistamines, such as benadryl or pyribenzamine; and hormonal extracts such as enterogastrone. Amino acids have also been used for their antacid value in protein deficiency.

Recent investigations by Dragstedt, and his associates, have advanced evidence to support the view that peptic ulcer may be due to the irritant and digestive action of hydrochloric acid, and also pepsin, on a susceptible area of the gastric mucosa. They reported striking improvement in patients with chronic ulcers following vagus nerve section.

Classification.—Gastric antacids may be classified in various ways. They may be classified on the basis of the manner in which they act—by direct neutralization of the hydrochloric acid of the stomach, or by adsorption of excess hydrogen ions leading to a higher pH and a resultant decrease in peptic activity. Included in the first group are sodium bicarbonate, magnesium oxide, tribasic calcium and magnesium phosphates, and magnesia and calcium carbonates. Those acting by their adsorbent action include aluminum hydroxide, aluminum silicate, colloidal magnesium silicate, and aluminum phosphate gel. A division into *systemic* and *nonsystemic* antacids is useful.

Systemic Antacids.—Systemic antacids are soluble and readily absorbed; they are capable of producing change in the pH of the blood and symptoms of alkalosis. If sodium bicarbonate is taken orally the hydrochloric acid of the gastric contents is neutralized, with the production of sodium chloride and carbon dioxide. Even if a systemic antacid is not in excess, indirectly it causes a rise in the bicarbonate content of the blood. Although the sodium bicarbonate leaves the stomach as sodium chloride, nevertheless, it is absorbed as bicarbonate, for it has prevented the neutralization of the acid gastric juice by the alkaline intestinal juices, which normally would have been reabsorbed as neutral chloride.

Nonsystemic Antacids.—The nonsystemic antacids neutralize the gastric contents, but they are not absorbed and do not tend to cause systemic alkalosis. Magnesium oxide, a typical nonsystemic antacid, forms magnesium chloride in the stomach. In the intestine magnesium chloride reacts with sodium bicarbonate to form magnesium carbonate which is relatively insoluble. The sodium chloride formed is reabsorbed. The magnesium salt and also the magnesium ion are slightly absorbed by the intestine, therefore are excreted primarily by the bowel. Sufficient magnesium salt is in solution to cause a mild catharsis.

The *theoretical ideal antacid* should possess the following properties:

1. It should be tasteless and not astringent to the mucosa of the mouth.
2. It should be efficient—a small amount of agent should neutralize a large amount of acid.
3. It should be neither constipating nor laxative.
4. It should be insoluble so as not to leave the stomach too quickly.
5. The antacid should be nearly neutral itself and should neutralize acid without liberation of carbon dioxide.
6. It should have a prolonged action and not stimulate a secondary acid rise.
7. It should be poorly absorbed, but, if absorbable, it should be nontoxic.
8. It should be low in cost, as medication usually must be continued for a considerable period of time.

COMMONLY USED ANTACIDS

The use of antacids in the treatment of gastric and duodenal ulcers has declined to some extent in recent years. Nevertheless these preparations are useful in the treatment of the ambulatory patient, but as in the case of dietary therapy, it is far from certain that the effectiveness of the alkalies is measured solely by their antacid neutralization capacity. Some of the commonly used antacids are given in Table VII. The doses are average and can be varied in inverse proportion to frequency of administration. Some clinicians recommend much smaller doses than stated below.

Sodium Bicarbonate

Sodium bicarbonate is widely used as a gastric antacid despite the fact that it has many disadvantages. It represents a typical systemic antacid. It is readily soluble and absorbable and acts rapidly to relieve symptoms associated with the presence of excess hydrochloric acid. The duration of its action is short and it leaves the stomach and is reabsorbed in the intestinal tract. Its sodium ion is absorbed, and in the presence of kidney disease alkalosis may result. In susceptible persons it may cause diarrhea. On interaction with gastric hydrochloric acid carbon dioxide is released with annoying belching and uncomfortable increase in intragastric tension. Its use in peptic ulcer is not recommended.

Sodium bicarbonate has been used in combination with calcium carbonate and magnesium oxide in proportions of 3 or 2 to 1, but this procedure offers questionable advantages. Calcium carbonate and magnesium carbonate may be used in combination so that the constipating and laxative effects neutralize each other. If bismuth subcarbonate (or subgallate) be added for its demulcent action, a rather effective combination is obtained.

TABLE VII

PROPERTIES OF ANTACIDS

ANTACID	DOSE	FAVORABLE PROPERTIES	UNFAVORABLE PROPERTIES	ACID NEUTRALIZATION'S RELATIVE EFFICIENCY
Sodium Bicarbonate	2 Gm.	Strong acid neutralizer	Liberates CO_2 in stomach; causes "acid rebound"; most likely to cause alkalosis; short action	100
Magnesium Oxide	0.25 to 2 Gm.	Strong acid neutralizer	Diarrhea; causes "acid rebound"	372
Calcium Carbonate	1 to 2 Gm.	Strong acid neutralizer	Liberates CO_2 in stomach; causes some "acid rebound"; long use may cause alkalosis; constipates	177
Magnesium Carbonate	0.6 to 2 Gm.	Strong acid neutralizer	Liberates CO_2 in stomach; causes some "acid rebound"; long use may cause alkalosis; laxative	--
Magnesium Trisilicate	1-4 Gm.	Moderate and slow acid neutralization; long-continued action; no alkalosis	On the basis of clinical results, this may be less effective than other preparations	100
Tribasic Calcium Phosphate	2 Gm.	Little systemic alkalinization	Some "acid rebound"; slightly constipating	--
Bismuth Subcarbonate	1 to 4 Gm.	Good demulcent; no "acid rebound"	Weak acid neutralizer; constipates	19
Aluminum Hydroxide Gel	4-15 cc.	Moderate acid neutralizer; good demulcent and astringent action; little "acid rebound"; no alkalosis	Constipates; expensive; may interfere with PO_4 absorption	13
Tribasic Magnesium Phosphate	1-5 Gm.	No systemic alkalinization; neutralizes excess acid	Slightly laxative	--
Mucin	2.5 Gm. repeated	Demulcent; no alkalosis; minimum effect on physiological functions; no "acid rebound"	Limited neutralizing action	--

℞

Calcium Carbonate	60.00 Gm. (℥ij)
Magnesium Carbonate	60.00 Gm. (℥ij)
Bismuth Subcarbonate	120.00 Gm. (℥iv)

M. Sig.: One teaspoonful two to four times daily one hour p.c. as directed.

Magnesium Salts

The oxide (0.25 Gm.), carbonate (0.25 Gm.) and the hydroxide (4 to 10 cc. magnesia magma) are commonly used antacids. They all have considerable combining power for acid, but are weak alkalies. They are valuable in treating *peptic ulcer* and *hyperacidity*.

MAGNESIUM OXIDE is a mild saline laxative and when used for antacid effects, the patient may complain of diarrhea. It is the most powerful antacid of the group. It causes the highest secondary acid rise. As an antacid in peptic ulcer, hyperacidity, etc., the following prescription is recommended:

℞

Atropine Sulfate	0.01 Gm. (gr.⅙)
Bismuth Subnitrate	
Magnesium Oxide	
Calcium Carbonate	
Sodium Bicarbonate	āā 30.00 Gm. (℥j)

M. Make into 30 papers.
Sig.: One powder in water two hours after meals.

MAGNESIUM CARBONATE is also laxative in action and causes a secondary acid rise. As in the case of sodium bicarbonate the evolution of CO_2 is a decided disadvantage.

Calcium Salts

CALCIUM CARBONATE is a good antacid and were it not for its constipating action and for its release of CO_2 in the stomach, it would approach the ideal in antacid therapy. Calcium carbonate (chalk) is usually administered in 1 gram doses of the precipitated calcium carbonate or the prepared chalk. Excessive doses are harmless and furnish protective action to irritated mucosa. Calcium carbonate is insoluble in water and may be given in larger doses than sodium bicarbonate. It does not readily cause alkalosis.

Limewater is used in the artificial feeding of infants. Externally, lime liniment is an old remedy for burns. Calcium carbonate and prepared chalk are sometimes used externally.

In treatment of hyperacidity:

℞

Magnesium Oxide	16.00 Gm. (℥iv)
Precipitated Calcium Carbonate	16.00 Gm. (℥iv)
Peppermint Oil	0.30 cc. (♏v)

M. Sig.: Level teaspoonful in a glass of milk two hours after meals.

Magnesium Trisilicate

To Dr. N. Mutch, Guy's Hospital, and Lecturer and Examiner in Pharmacology, London University, goes the credit for the discovery of the unique therapeutic properties of magnesium trisilicate.

Hydrated magnesium trisilicate has the empirical formula, $2MgO.3SiO_2.nH_2O$. It is a tasteless white powder, insoluble in water. Mutch states that magnesium silicates were mentioned by Dioscorides in his *Materia Medica* and that usually as soapstone these were prized by the "geophagists either as table delicacies or as famine food."

Pharmacological Action.—Mutch (1937) states that in hyperacid conditions the use of medicinal trisilicate results in the continuous control of gastric acidity. Two factors make this possible. First, the slowness of action of the drug. At body temperature a substantial secondary neutralization continues for more than an hour after the quick initial neutralization has occurred. Second, the nontoxicity of this compound permits administration of adequate doses to compensate for the continuous loss through the pylorus. This compound acts as an adsorbent as well as an antacid and, although it neutralizes free acid, an excess of it will not render the stomach contents alkaline to such an extent as to destroy peptic activity. Mutch estimates that the daily dosage would be 2.5 grams or a 0.5 gram dose five times daily.

Of great interest to the clinician is the fact that magnesium trisilicate is an effective adsorbent. Tests show that it is effective in adsorbing certain alkaloids, colloids, bacterial toxins, putrefactive amines, and food poisons; for example, the adsorptive capacity of magnesium trisilicate for bacterial toxins is such that one gram of the silicate removes at least 140 M.L.D. (mouse units) of tetanus toxin.

Mutch (1936) after completing extensive investigations on the therapeutic use of magnesium trisilicate in chronic peptic ulcer, concluded that magnesium trisilicate "quite clearly supplied an effective medicinal control for all types of ulcers. The special features of its employment are: (1) The combination of three therapeutic actions in a single substance; namely, antacid, antiseptic, and antitoxic, each of which fulfills a useful role in the stomach and duodenal bulb. (2) A sustained action whereby hydrochloric acid, destructive ferments, and toxins can be removed continuously for several hours after the administration of a single dose. (3) The possibility of a local therapy at the ulcer base independently of the changes occurring in the gastric contents as a whole. (4) Freedom from risk of inducing toxic alkalosis."

Mann (1937) states: "Clinical experience to date has confirmed its value and it bids fair to supplant all other alkalies in the treatment of peptic ulcer."

Therapeutic Uses.—Magnesium trisilicate is recommended for the relief of gastric hyperacidity and pain in gastric and duodenal ulcer. It has also been recommended in illness due to various poisons, toxins, and alkaloids, as well as in so-called "intestinal allergy."

Dosage.—Administer 1 to 4 Gm. before meals. The single dose and the frequency of repetition depend on the degree of acidity and the relief afforded.

Tribasic Calcium Phosphate

Tribasic calcium phosphate, $Ca_3(PO_4)_2$, has been proposed as an antacid. It has the advantage over magnesium hydroxide and sodium bicarbonate, in that, being less soluble, it tends to neutralize the excess of acid in the stomach but produces less systemic alkalization. Some of the calcium is absorbed, hence this salt may be used for its therapeutic effect. The tribasic calcium phosphate is somewhat constipating.

Bismuth Compounds

The subgallate, and the subcarbonate, in doses of 0.15 to 2 grams, and the magma of bismuth, 4 cc., are used to lessen hypersecretion, as demulcents in *peptic ulcer,* and to check nausea and vomiting. The action may be a protective and demulcent type and not an antacid type of reaction. Some say its action is due to its astringent properties. Combined with sodium bicarbonate it has gained favor among the laity as bismuth and soda.

Bismuth compounds may be administered in large amounts, but when applied to raw surfaces, bismuth poisoning may occur. The most striking symptom is the black discoloration of the gums, similar to the lead line of lead poisoning. Other symptoms, such as swelling of the tongue, dysphagia, salivation, and gastrointestinal upset, are common.

Aluminum Hydroxide Gel

This preparation is an aqueous suspension containing between 3 and 4.2 per cent of aluminum oxide, primarily in the form of aluminum hydroxide.

Pharmacological Action.—Aluminum hydroxide gel is an effective gastric antacid which neutralizes the hydrochloric acid of the stomach by chemical neutralization. It is not absorbed from the gastrointestinal tract to any appreciable extent and is therefore nontoxic when administered orally. Its astringent action may produce a constipating effect. It has the advantages that it does not increase the pH of the gastric juice so as to interfere with peptic digestion, does not stimulate compensatory increase in free gastric acidity, and does not produce systemic alkalization. Its mild astringent and demulcent properties may be of some value in the local action on peptic ulcer. Some evidence is available that some of its effectiveness may be due to its tendency to increase mucin secretion.

The amphoteric action of aluminum hydroxide is of no significance clinically because it reacts as an acid only at a pH above 9, a reaction not encountered in the gastrointestinal tract. It is thought that the acid salt aluminum chloride formed in the stomach is reconverted to the original compound or other aluminum compounds by reaction with the alkaline contents of the intestines, and the chloride is reabsorbed.

Aluminum hydroxide gel may possess adsorptive properties but no conclusive evidence is available to show that it adsorbs acids, toxins, bacteria or gases. There is some evidence available, however, to suggest that the administration of aluminum compounds may interfere with the absorption of certain minerals and can produce a phosphorus deficiency in the presence of pancreatic deficiency. This objection does not contraindicate its use in peptic ulcer and gastric hyperacidity, since the diet in these conditions is usually rich in phosphorus. Aluminum phosphate has been suggested especially in patients with diarrhea.

Therapeutic Uses.—Aluminum hydroxide gel is indicated for the treatment of *peptic ulcer* to promote healing, relieve pain, and control hemorrhage. It is also useful for the control of *gastric hyperacidity.* It may be of some value in the treatment of other gastrointestinal conditions.

Administration.—Oral: Aluminum hydroxide gel is given orally in doses of from 4 to 8 cc. in one-half glass of water or milk every two to four hours, or one-half to one hour after meals. *By Drip Apparatus:* It may be administered by the method of continuous drip by stomach tube. Dilute 1 part to 3 parts of water and administer 1,500 cc. of diluted suspension at the rate of 15 to 20 drops per minute.

Tribasic Magnesium Phosphate

Tribasic magnesium phosphate, $Mg_3(PO_4)_2$, is a useful gastric antacid. It has the advantage over magnesium hydroxide and sodium bicarbonate in that, being soluble, it neutralizes the excess of acid in the stomach, but does not produce systemic alkalization. It possesses some laxative action. *Dosage:* Administer 1 to 5 Gm. (15 to 75 grains) orally.

Gastric Mucin

Mucin is a preparation obtained by precipitating with 60 per cent alcohol the supernatant liquid from pepsin-hydrochloric acid digestion of hog stomach linings. Mucin cannot produce alkalosis, and apparently has a minimum effect on gastrointestinal functions. Its demulcent action and its adsorbent mode of action distinguish it from the antacids. One gram of dried mucin combines with approximately 15 cc. of N/10 HCl. Clinical reports indicate that it is useful in ulcer therapy. The average dose is 2.5 Gm. given at two-hour intervals.

Choice of Antacid

In view of the many contradictory statements in the literature and the variable responses exhibited by different patients, it is difficult to name the best antacid. If complete neutralization is desired frequent (i.e., hourly) alkali therapy with a strong neutralizer like magnesium oxide is indicated. If antacids are to be given only three to six times a day, the slower but longer-acting aluminum hydroxide gel and magnesium trisilicate may be used. In most ambulatory cases, the more infrequent dosage is effective and can be given one hour after food in place of the first interval feeding. The following plan might be used for the average ambulatory patient.

Schedule:

8:00 A.M.	Breakfast (milk, cream, eggs, cooked cereal)	
9:00 A.M.	Aluminum Hydroxide	8 cc.
10:30 A.M.	Milk	120 cc.
12-1:00 P.M.	Noon Meal (mashed potatoes, puréed vegetables, custards, rice pudding, well-cooked and ground meat)	
2:00 P.M.	Aluminum Hydroxide	8 cc.
3:30 P.M.	Milk and cream	
5:30-6:30 P.M.	Evening Meal (Bland foods)	
7:30 P.M.	Aluminum Hydroxide	8 cc.
9:00 P.M.	Milk and cream	
11:00 P.M.	Milk and cream	
Before retiring	Aluminum Hydroxide	8 cc.
At night	Every patient should have an antacid preparation to alleviate any nocturnal symptoms.	

Some clinicians believe that alkalies should be given only when dietetic regimen and ample rest are ineffective in relieving symptoms. Then the alkalies should be given in small doses: for example, 0.65 Gm. magnesium trisilicate alone; or a combination of 0.32 Gm. calcium carbonate, 0.32 Gm. calcium phosphate, 0.32 Gm. magnesium trisilicate and 0.32 Gm. magnesium oxide, in half a glass of water, sipped slowly, fifteen to twenty minutes after each feeding.

PREPARATIONS

Sodium Bicarbonate, *Sodii Bicarbonas*, U.S.P., B.P. (Baking Soda). $NaHCO_3$ *Dosage:* 2 Gm. (30 grains).

Magnesium Oxide, *Magnesii Oxidum*, U.S.P. *Dosage:* antacid, 0.25 Gm. (4 grains); laxative, 4 Gm. (60 grains).

Magnesia Magma, *Magma Magnesiae*, U.S.P. (Milk of Magnesia). A suspension of magnesium hydroxide (about 7.5%) in water, forming a thick white liquid. *Dosage:* antacid 4 cc. (1 fluidrachm); laxative, 15 cc. (4 fluidrachms). *Mistura Magnesii Hydroxidi*, B.P. 4-16 ml. (60-240 min.).

Precipitated Calcium Carbonate, *Calcii Carbonas Praecipitatus*, U.S.P. *Dosage:* 1 Gm. (15 grains). *Calcii Carbonas*, B.P. *Dosage:* 1-4 Gm.

Magnesium Carbonate, *Magnesii Carbonas*, U.S.P. Hydrated magnesium carbonate, equivalent to about 41 per cent MgO. *Dosage:* antacid, 0.6 Gm. (10 grains); laxative, 8 Gm. (2 drachms).

Magnesium Trisilicate, *Magnesii Trisilicas*, U.S.P. *Dosage:* 1 Gm. (15 grains).

Magnesium Trisilicate Tablets, *Tabellae Magnesii Trisilicatis*, U.S.P. The usual sizes contain 0.3 Gm. and 0.5 Gm.

Tribasic Calcium Phosphate, *Calcii Phosphas Tribasicus*, N.F. *Dosage:* 1 Gm. (15 grains).

Bismuth Subcarbonate, *Bismuthi Subcarbonas*, U.S.P. *Dosage:* 1 Gm. (15 grains). *Bismuthi Carbonas*, B.P. 0.6-2 Gm. (10-30 grains).

Bismuth Subgallate, *Bismuthi Subgallas*, N.F. *Dosage:* 1 Gm. (15 grains).

Aluminum Hydroxide Gel, *Gelatum Alumini Hydroxidi*, U.S.P. Contains about 4% Al_2O_3. *Dosage:* 8 cc. (2 fluidrachms).

Tribasic Magnesium Phosphate, *Magnesii Phosphas Tribasicus*, N.F. *Dosage:* 1 Gm. (15 grains).

Gastric Mucin, N.N.R. *Dosage:* 2.5 Gm. (37.5 grains).

DIGESTANTS

Digestants, such as hydrochloric acid, pepsin, bile, and pancreatin, are used to promote the process of digestion in the gastrointestinal tract. The digestion of food in the alimentary canal is accomplished mainly by the action of digestive ferments or enzymes. They are of great importance in the body, but have a limited usefulness in therapy.

Hydrochloric Acid

Hypochlorhydria, a deficiency in the secretion of hydrochloric acid, occurs in from 10 to 15 per cent of the general population. Achlorhydria or absence of free hydrochloric acid in gastric juice is observed in such conditions as gastric carcinoma, gastritis, pernicious anemia, and numerous other conditions. Achlorhydria is also encountered in apparently normal individuals.

Hydrochloric acid (HCl) is an aqueous solution containing not less than 35 per cent nor more than 37 per cent of hydrochloric acid. It is incompatible with alkaline carbonates, chlorates, silver salts, lead salts, etc.

Pharmacological Action.—**Hydrochloric acid converts pepsinogen to active pepsin and supplies the proper acid medium essential for this enzyme activity. Acid apparently plays an important role in the control of the normal emptying time of the stomach. Hydrochloric acid increases the pyloric peristalsis; it closes the cardiac and opens the**

pyloric sphincter until the intestinal juices neutralize the acid (Cannon, 1911). Hydrochloric acid favors protein digestion, and also serves as an activator of pancreatic secretions and bile. Due to its antiseptic action, hydrochloric acid checks fermentation and putrefaction in the stomach and intestine, thus preventing organisms which enter through the mouth from contaminating the alimentary tract, especially the gall bladder, the appendix, and the colon.

Therapeutic Uses.—Hydrochloric acid is indicated in the treatment of *gastric achlorhydria.* In the past, 2 to 4 cc. of dilute hydrochloric acid has been commonly prescribed before meals. This amount is probably insufficient and at least 15 to 20 cc. of dilute hydrochloric acid should be administered if any real substitution therapy is to be attained. The acid may be prescribed in solid form as glutamic acid hydrochloride.

When hydrochloric acid solutions are given, the teeth should be protected by the use of a glass rod. The solutions should be very dilute. If large amounts of hydrochloric acid are prescribed, the administration of fruit juices or sodium citrate is advisable in order to prevent acidosis.

Pepsin

Pepsin, a substance containing a proteolytic enzyme, is obtained from the glandular layer of the fresh stomach of the hog. It is assayed to be of such activity that it digests about 3,500 times its weight of egg albumen. It occurs in pale transparent scales or as a powder; it is soluble in water and insoluble in alcohol. It is inactive in the presence of 0.5 per cent hydrochloric acid, and is inert in the presence of alkalies.

Action and Uses.—Pepsin is used only in acid medium, and is indicated in the treatment of stomach diseases when the gastric juice is deficient. The gastric juice usually, however, contains sufficient pepsin for gastric digestion. Since food leaves the stomach rapidly and enters the alkaline intestine, pepsin will soon become inactive. Bastedo expresses his opinion of pepsin as follows: "What a wonderful substance to have so little use in medicine." Following a study of the use of digestive enzymes in therapeutics the members of the Gastro-Enterological Association concluded in a questionnaire that gastric enzymes are of minor importance in therapeutics.

Bile, Bile Salts, and Bile Acids

Human and ox biles are composed chiefly of the bile salts (sodium glycocholate, sodium taurocholate), bile pigments, cholesterol, and lecithin. The bile salts probably account for the major pharmacological properties of bile. Sodium glycocholate and sodium taurocholate are found to the extent of about 3 per cent in fresh ox bile.

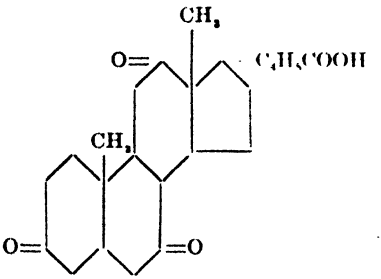
Action and Uses.—Bile is essential for normal digestion of fats and the absorption of fatty acids. It aids digestion by emulsifying fats and by activating pancreatic lipase. Bile is generally credited with a slight antiseptic and laxative action. The bile salts are essential for the optimal absorption of fat-soluble substances, such as carotene, vitamin A, vitamin D, and vitamin K. They also stimulate the secretory activity of the liver, increasing both the fluid and solids of the bile.

Orally, bile salts *aid digestion and absorption,* and after the bile salts are absorbed they act as *choleretics* and facilitate biliary drainage. Their rationale is doubtful in *obstructive jaundice.* The value of bile salts in conjunction with the oral administration of vitamin K is discussed under Vitamin K. Ivy and Berman (1939) recommend a copious flow of bile of low viscosity in the treatment of *disease of the biliary*

tract unassociated with acute hepatitis. Bile salts have also been recommended for their choleretic action in the treatment of *functional hepatic insufficiency, hepatic jaundice,* and in *cirrhosis* and *chronic passive congestion of the liver.* Bile salts have also been used to outline bile ducts at operation; in *cholecystography,* to accelerate the appearance of the gall bladder shadow and hasten the removal of residual tetraiodophenolphthalein from the biliary apparatus. The dose is 0.5 to 2.0 grams.

Dehydrocholic Acid

Dehydrocholic acid is an oxidation product of cholic acid derived from natural bile acids. The formula is



Dehydrocholic acid is useful for its ability to increase the volume of the bile (hydrocholeretic action); however, it has no cholagogue action. Its effect on the secretion of bile constituents (choleretic action) is uncertain.

Dehydrocholic acid may be of value due to its hydrocholeretic action, to encourage drainage of the bile ducts and thus discourage infection of these structures. This compound may also be employed to encourage maintenance of T-tube surgical drainage of an infected common duct and as an aid in the removal of small stones. It may also be of value in outlining the bile ducts at operation and of hastening the appearance of the gall bladder shadow and hastening the removal of residual dye from the biliary tract in cholecystography.

There is some evidence that dehydrocholic acid is useful in the treatment of arsenical and other forms of toxic hepatitis and of hepatic dysfunction, and as a diuretic, alone or in combination with the mercurials, in the treatment of ascites due to hepatic congestion in heart disease and liver damage. The drug is contraindicated in complete mechanical biliary obstruction. Furthermore, its use in severe hepatitis may also be questioned on the ground that the hydrocholeretic effect may aggravate the condition. *Dosage:* Administer from 0.25 to 0.5 Gm. (3¾ to 7½ grains) two to three times daily after meals for a period of four to six weeks.

SODIUM DEHYDROCHOLATE.—The action and uses of the sodium salt of dehydrocholic acid are the same as those given for dehydrocholic acid. It is also used for determination of the circulation time. It is contraindicated for such use in the presence of bronchial asthma. *Dosage:* Administer drug by vein, one injection being given on each of three successive days. The usual initial dose consists of 5 to 10 cc. of the 20 per cent solution; the second and third, of 10 cc. *Circulation Time:* For determination of arm to tongue circulation time, inject rapidly (2 to 3 seconds) 3 to 5 cc. through an 18 gauge needle

into a cubital vein. Place subject in a supine position during injection. Take time from beginning of injection to the perception of a bitter taste. The average normal range is from nine to sixteen seconds.

Pancreatin

Pancreatin is an enzyme preparation made from the pancreas of the hog or ox and contains principally amylopsin, trypsin, and steapsin. It is a cream-colored powder standardized to convert not less than 25 times its own weight of starch into soluble carbohydrates, and 25 times its weight of casein into proteoses. It is rendered inactive by acids.

Action and Uses.—It is used chiefly for the predigestion of protein and starchy foods. It is rarely prescribed as such, but is often employed in the form of various proprietary prescriptions. When prescribed it should be administered in enteric pills. It is occasionally used to assist gastric digestion in achlorhydria, but the administration of dilute hydrochloric acid seems preferable. In proved pancreatic deficiency pancreatin is indicated.

Pancreatic steatorrhea, a chronic fatty diarrhea, may be caused by deficient pancreatic secretion. Fat and protein are poorly tolerated and should be reduced in the diet. Amino acids are indicated and also large doses of *fresh pancreatin* (up to 24 Gm. daily). This dosage may be reduced after improvement. Lipocaic and bile salts are of no value.

Pancreatin is used chiefly for *peptonizing* milk for invalids. For this purpose 0.4 gram of pancreatin and 2 grams of sodium bicarbonate are mixed with 120 cc. of water, and 500 cc. of whole milk are added. This is kept at a temperature of 104° to 110° F.; for use by mouth, terminate action in twenty minutes by boiling.

Preparations

Diluted Hydrochloric Acid, *Acidum Hydrochloricum Dilutum*, U.S.P., B.P. HCl about 10 %. *Dosage:* 4 cc. (1 fluidrachm).

Pepsin, *Pepsinum*, N.F. *Dosage:* 0.5 Gm. (8 grains).

Ox Bile Extract, *Extractum Fellis Bovis*, U.S.P. Contains an amount of the sodium salts of ox bile acids equivalent to not less than 45 per cent of cholic acid. *Dosage:* 0.3 Gm. (5 grains). *Extractum Fellis Bovini*, B.P., 0.3-1 Gm. (5-15 grains).

Dehydrocholic Acid, N.N.R. An oxidation product of cholic acid derived from natural bile acids. *Dosage:* from 0.25 to 0.5 Gm. (3¾ to 7½ grains) two to three times daily after meals for a period of four to six weeks.

Sodium Dehydrocholate, N.N.R. The sodium salts of dehydrocholic acid. *Dosage:* Administer intravenously one injection on each of three successive days. First dose 5 to 10 cc. of 20 per cent solution; the second and third, 10 cc.

Pancreatin, *Pancreatinum*, U.S.P. *Dosage:* 0.5 Gm. (7½ grains).

LOCALLY ACTING EMETICS

Emetics are drugs or medicines that cause vomiting. A century ago local emetics were very extensively employed in medicine, but their use has steadily declined. Emesis may be caused by locally acting drugs such as copper sulfate, mustard, etc. Apomorphine is an excellent centrally acting emetic.

Mode of Action.—Local emetic action is produced reflexly by irritation of the gastric mucosa. Not every form of gastric irritation results in vomiting; the kind, rather than intensity, of irritation is important. Ipecac produces vomiting by both central and local action.

Therapeutic Uses.—Emetics are employed for evacuation of the stomach in *acute poisoning* and in *acute indigestion.* They are indicated when gastric lavage is not practical. They are *contraindicated* in caustic poisoning and in conditions such as hernia, heart defects, pregnancy, and general debility.

The commonly used emetic drugs and their dosages are:

Mustard	4-8 Gm. (3i-ij) in water.
Ipecac	4 Gm. (3j) or 15 cc. (4f3) of the syrup, in water.
Copper Sulfate	0.3 Gm. (gr.v) in water.
Zinc Sulfate	1 Gm. (gr.xv) in water.

Mustard is the safest but also the least effective locally acting emetic. A teaspoonful of powdered mustard in a cup of warm water, repeated every fifteen minutes, is the usual method of administration.

Ipecac is uncertain in action and is quite depressing. The emetic action of ipecac is due to the presence of two irritant alkaloids, emetine and cephaeline. Ipecac and emetine produce prolonged nausea and sweating. Due to its delayed action it is unsuitable for treatment of poisoning; however, subemetic doses are used extensively as *expectorants* and *sudorifics.*

Both *copper and zinc sulfate* cause vomiting by provoking the vomiting reflex. They are absorbed rapidly and cause little depression. Vomiting occurs in a very few minutes. They are especially useful to empty the stomach of noncorrosive poisons. The emetic dose of copper sulfate is 0.25 Gm. in 1 per cent solution, that of zinc sulfate is 1 to 2 Gm. They may be repeated in 15 minutes if necessary.

Salt water (2 tablespoonfuls to 8 ounces of warm water), or even *warm water,* may be useful in causing emesis when the patient is already disposed to vomiting. *Mechanical tickling* of the fauces, by inserting the finger or some instrument in the pharynx, may be effective. *Avoid* emetics in cases of narcotic or convulsive poisonings. Use stomach tube unless convulsions are present or imminent, or unless a corrosive has been swallowed.

Preparations

Ipecac, *Ipecacuanha,* U.S.P., B.P. Rhizome and root, yielding not less than 2 per cent of ether-soluble alkaloids. *Dosage:* emetic, 0.5 Gm. (7½ grains).

Ipecac Fluidextract, *Fluidextractum Ipecacuanhae,* U.S.P. Ipecac (100%), yielding about 2 per cent of ether-soluble alkaloids. Absolute alcohol content about 30 per cent. *Dosage:* Emetic, 0.5 cc. (8 minims).

Ipecac Syrup, *Syrupus Ipecacuanhae,* U.S.P. Fluidextract of ipecac (7%) in glycerin and syrup. *Dosage:* emetic, 8 cc. (2 fluidrachms).

EXPECTORANTS

An expectorant is a drug which aids in the removal of exudate or mucus from the trachea, bronchi, and lungs. Some extend the term to include all remedies that quiet coughing.

A complete classification of expectorants is hardly indicated at this time. A large variety of them are not generally needed by the aver-

age physician. Useful expectorants include the following: Ipecac Fluidextract, Ipecac Syrup, the Iodides, Ammonium Chloride, Terpin Hydrate, Codeine, and a few official expectorant mixtures.

Ipecac Fluidextract, Ipecac Syrup, and the Iodides are the most useful in conditions in which the bronchi are blocked by mucus (e.g., asthma). Ipecac causes nausea and vomiting and induces a peristaltic action in the trachea (Rutner, 1947), which releases the obstructing plugs. For infants and small children, administer ½ to 1 teaspoonful (2 to 4 cc.) of Ipecac Syrup. Larger doses may be necessary. In older children, and adults, repeated doses may be given if needed.

For children, Glycyrrhiza Syrup is an excellent vehicle for Ipecac Syrup. Raspberry Syrup, Tolu Balsam Syrup, and Cacao Syrup are also useful.

Ammonium Chloride and the Iodides are useful against thick secretions. The Iodides, being partially eliminated in the bronchi, apparently liquefy the secretions as the result of a slight irritation of the mucous membranes.

The following prescription is from the Mayo Clinic:

℞

Potassium Iodide	15.00 cc.	(ʒss)
Lobelia Fluidextract	1.20 cc.	(mxx)
Hyoscyamus Fluidextract	1.20 cc.	(mxx)
Glycerin	20.00 cc.	(ʒv)
Simple Elixir q.s. ad	240.00 cc.	(ʒviij)

M. Sig.: One teaspoonful in water three times daily after meals.

Ammonium Chloride is an efficient expectorant in combating cough. The following prescription is useful:

℞

Ammonium Chloride	15.00 cc.	(fʒiv)
Citric Acid Syrup	30.00 cc.	(fʒj)
Water q.s. ad	120.00 cc.	(fʒiv)

M. Sig.: Give one teaspoonful every two hours.

Certain antiseptic expectorants have been used, but it is highly improbable that they are eliminated in the bronchial secretions in sufficient quantity to give antiseptic action. Such drugs include creosote, guaiacol, terpin hydrate, and others.

The anodyne expectorants include morphine, dilaudid, and codeine. Codeine is the most commonly used of this group. Its action will be discussed under Morphine.

Preparations

Ipecac Preparations—see under Emetics.

Ammonium Chloride, *Ammonii Chloridum*, U.S.P.—NH_4Cl. *Dosage:* 0.3 Gm. (5 grains) in solution as expectorant; from 3 to 6 Gm. daily as diuretic, being careful to avoid acidosis.

Potassium Iodide, *Potassii Iodidum*, U.S.P.—KI. *Dosage:* 0.3 Gm. (5 grains); antisyphilitic, 2 Gm. (30 grains).

Terpin Hydrate, *Terpini Hydras*, N.F. *Dosage:* 0.25 Gm. (4 grains).

Compound Opium and Glycyrrhiza Mixture, *Mistura Opii et Glycyrrhizae Composita*, N.F. (Brown Mixture). *Dosage:* 4 cc. (1 fluidrachm).

Compound Squill Syrup, *Syrupus Scillae Compositus*, N.F. (Hive Syrup).
Dosage: 2 cc. (30 minims).
Expectorant Mixture, *Mistura Pectoralis*, N.F. (Stoke's Expectorant).
Dosage: 4 cc. (1 fluidrachm).

ADSORBENTS

The therapeutic use of adsorbents in the alimentary canal involves a complicated interaction of compounds, the results of which often cannot be controlled, and the reactions taking place are little understood. An adsorbent is a substance which has the power of condensing and holding a gas or other substance upon its surface. The usual aim in administering adsorbents is the removal of bacteria and bacterial toxins or toxic products of protein digestion.

Mode of Action.—The usefulness of adsorbents in the digestive tract, with their varying reactions throughout their course, is limited because adsorbents may act as acids or alkalies, or as amphoteric substances. Since the reaction of the digestive tract varies, one cannot predict the results which may follow their use. It must be remembered that large doses of these highly adsorbent materials may also remove such substances as vitamins, enzymes, and minerals. In addition, adsorbents may produce a partial obstruction of the intestine; records show that kaolin may cause intestinal perforations.

Although many substances exhibit adsorptive action, only charcoal, kaolin, and bentonite have been utilized for this purpose to any extent in medicine.

Charcoal

Charcoal is a black, odorless, tasteless, and insoluble powder, produced from the destructive distillation of various organic materials. Later, it may be treated to increase its adsorptive power.

Action and Uses.—Charcoal is an excellent adsorbent, having the power to adsorb various kinds of organic acids and drugs. This substance is credited with the ability of removing mercury salts and strychnine from the walls of the stomach, of removing all the products of intestinal putrefaction from urine shaken with it, and of preventing the poisonous action of alkaloids on excised rabbit's intestine. Charcoals that are wetted by water easily are thought to be more efficient in adsorbing gases than those resistant to wetting.

Charcoals are employed in the treatment of certain forms of *dyspepsia*, and in testing intestinal activity. Charcoal, up to 80 grams or more daily, may be added to kaolin or be given separately. Animal charcoal is preferred to vegetable charcoal, as its particles are smaller and less irritating. The exact medical status of this compound is still unknown. It is employed internally, alone or with other drugs. It may well be administered in gelatin capsules in three- to five-grain amounts per capsule.

Kaolin

Kaolin (aluminum silicate, china clay, or bolus alba) is a clay that has been used for centuries in China for summer diarrheas and cholera. It is a very fine insoluble powder.

Action and Uses.—Kaolin adsorbs the toxins of some organisms and thus lessens their absorption into the body. The powder also forms a thin coating over the intestinal mucosa and thus protects it from inflammation, and also lessens absorption from the gut. Kaolin is a negatively charged colloid and therefore adsorbs positively charged

substances. It possesses no direct disinfectant action on the gut. The beneficial action of kaolin may depend on several factors. Some suggest that the antidiarrheic action of kaolin is due to the removal of colloids from the intestinal fluid, thus decreasing its osmotic pressure and consequently allowing rapid absorption of this fluid by the bowel.

Rogers recommends the following treatment for cholera: The frequent administration of potassium permanganate (0.1 Gm. doses) by mouth to destroy the bacterial toxins; kaolin in large amounts orally to reduce the absorption of toxins; then intravenous injection of hypertonic saline to combat dehydration and loss of chlorides.

In food poisoning (Salmonella) after the stomach is emptied many clinicians recommend kaolin (8 Gm.) stirred in a glass of water and sipped as frequently as possible. This treatment is preferable to the usual method of administering castor oil.

In addition to the use of charcoal and kaolin, there are other adsorbents which are of definite value for use in the digestive tract. Hess found *Fuller's earth* especially valuable in treating intestinal disorders in infants. *Aluminum hydroxide* is a particularly good adsorbent and has the advantage of being an amphoteric substance.

Bentonite

Bentonite is a variety of clay, hydrous aluminum silicate, occurring as a fine, colorless powder. It swells to about eight times its volume when added to water. Bentonite, as well as the other adsorbents, is of value in the treatment of mercuric chloride and alkaloid poisoning. Large quantities are indicated. Intestinal obstruction must be kept in mind.

The Clinical Use of Adsorbents.—Substances such as kaolin are worthy of trial in patients suffering from *food poisoning* or from *dysentery*. In these cases food is stopped and large doses of kaolin (50 to 100 Gm.) are administered in water every three hours until the number of movements begin to decrease. Kaolin in liberal amounts has been recommended for the treatment of *diarrhea*. In the case of idiopathic ulcerative colitis the kaolin must travel the length of the small intestine before reaching the seat of the trouble, and during this passage its beneficial properties are no doubt lost. Inert substances are contraindicated in the presence of diverticulitis because of the danger of perforation and obstruction. Finally, in the treatment of dyspepsia and conditions of autointoxication, the etiology of which we know little, the use of adsorbents is not warranted. Further clinical and laboratory investigation is needed before we can administer adsorbents intelligently.

Preparations

Activated Charcoal, **Carbo Activatus**, U.S.P. **Dosage:** 1 Gm. (15 grains).
Kaolin, **Kaolinum**, N.F., B.P.
Bentonite, **Bentonitum**, U.S.P.

CATHARTICS OR PURGATIVES

GENERAL DISCUSSION OF CONSTIPATION

Constipation may be defined as a *functional impairment in the inherent capacity of the colon to produce normally-formed stools at regular intervals*. This disorder affects about one-half of the patients complaining of digestive disorders. Nearly every one suffers occasionally from brief periods of constipation, while some persons are al-

ways constipated. It is difficult, however, to exaggerate the prevalent abuse of cathartics. The radio and press inform the layman of the disasters of intestinal toxemia, yet there is no evidence to show that harmful substances are absorbed from the colon in constipation.

Many of the discomforts caused by constipation may be due, not to intestinal autointoxication, but to mechanical disturbance of the sympathetic system. This view is thought to be substantiated in part by the fact that relief from constipation follows immediately after the bowels have moved and that the symptoms of toxemia rarely could disappear in so short a time. Also chronic constipation may exist without symptoms and similar symptoms may be produced by distention of the lower bowel.

Etiology.—The causes of constipation are complex. The following are the most common causes of the condition:

1. Diet irregularities, such as irregular meals, insufficient water drinking, food restrictions, and special restriction in the intake of fruits, vegetables, and coarse cereals, often cause constipation.

2. The habit of neglecting call to stool in early life is responsible in many cases. In later life the constant use of cathartics and enemas progressively weakens the normal bowel mechanism.

3. Psychic and nervous factors are important. Nervousness, worry, hurry, and anxiety tend to cause constipation.

4. Body habitus influences bowel regularity. Constipation is far more common in the tall thin person (asthenic), than in the short stocky individual (sthenic).

5. Colon anomalies, especially the redundant colon, tend to impair the formation of normal stools.

Types.—The following types of constipation are recognized:

1. *Atonic Constipation.*—This type is the most common in asthenic and thin persons. It may result from long and continued use of enemas and cathartics, or be due to a congenital muscular weakness.

2. *Spastic Constipation.*—This is the most common type. The distal part of the colon is usually involved. The condition begins usually by constant use of cathartics; gradually the effects of frequent purgation and the effects of high roughage diet produce a condition of chronic bowel irritation. This gradually causes loss of coordination and lack of correlation between the normal functions of the colon. Various segments of the colon respond differently; the proximal colon may be atonic and dilated, while the distal colon may be spastic and hyperirritant. There may be diarrhea or constipation, or the two conditions may alternate.

Spastic constipation is best treated by rest, bland diet, heat, and antispasmodics. The omission of cathartics is essential, as the colon is already overirritated.

3. *Rectal Spasm.*

4. *Ineffective Colonic Reflexes* due to lack of bulk and roughage.

5. *Loss of Defecation Reflex* through disregard of call to stool or from constant use of cathartics.

THERAPEUTICS OF CONSTIPATION

1. **General Hygiene.**—Regular hours for meals, proper mastication of food, and sufficient sleep are all means of treating the condition of chronic constipation.

2. **Psychotherapy.**—The patient should be informed that there is no danger from his trouble. The mental inhibition of bowel function must be eliminated by proper guidance in thinking.

3. **Reestablishment of Bowel Habit.**—The fecal matter is held in the descending colon. By the taking of food (especially breakfast) the peristaltic waves tend to urge the fecal column to the rectum. This tends to produce a desire to defecate, which is aided by voluntary as well as the involuntary muscles of defecation. By establishing a regular habit of defecation, about 30 minutes after breakfast, one produces astonishing results toward curing chronic constipation.

4. **Exercise.**—Outdoor exercise, such as walking, horseback riding, golf, etc., is an excellent prophylactic for constipation. An exercise that makes use of the abdominal muscles is valuable. Massage is a great help for those who do not desire to exercise.

5. **Hydrotherapy.**—Cold baths are of great value in atonic constipation. The cold tends to stimulate peristalsis and aids in producing an evacuation. Hot baths, or heat applied to the abdomen, induce relaxation which relieves the condition of spastic bowel.

6. **Diet.**—Fluids are valuable; one to two glasses of water before breakfast are recommended. An increased fluid intake remedies excessive dehydration of fecal matter in the colon. The diet may be further modified by the addition of roughage, such as bran, to increase peristalsis. In spastic conditions, such as spastic constipation and irritable colon, roughage is contraindicated.

MEDICAL THERAPY

In the use of cathartics the following rules must be kept in mind:

1. Cathartics tend to produce, rather than cure, constipation. The complete removal of the bowel contents leaves no residue to excite bowel movement.

2. Cathartics are contraindicated in spastic constipation, as they cause a greater spasticity.

3. Cathartics are contraindicated in acute abdominal pain, i.e., appendicitis, intestinal obstruction, and any acute abdominal condition.

4. There are indications for cathartics and when used the mildest drug suitable for the individual case should be selected.

5. Any general routine use of cathartics, such as following colds, etc., should be discouraged.

6. Certain cathartics are eliminated in the milk of nursing mothers and their effects upon the baby should be considered.

7. Cathartics are indicated in gastrointestinal upsets in children, for the removal of poisons from the intestines, in certain types of diarrhea, in the treatment of edema, and in cases of temporary constipation.

8. Before giving an active cathartic consider carefully the indications and contraindications. Decide whether the limited value of emptying the intestinal tract will offset the dehydration, discomfort, exhaustion, loss of nutrition, and loss of sleep which follow the administration of cathartics.

9. *Do not use cathartics to relieve gastrointestinal symptoms of unknown origin.*

Cathartics are drugs employed in medicine to evacuate the bowel of its contents. There is some evidence of a decreasing tendency on the part of physicians to prescribe cathartics. The ideal cathartic would be one that would act on the intestine and give no significant side reactions after absorption. More space has been allotted in this text

to cathartics than their medical usefulness warrants; however, a complete evaluation of them may clear up many misconceptions previously held.

The mechanism most commonly utilized in the treatment of constipation depends on the local actions of cathartic agents present within the lumen of the gut. *For all practical purposes cathartics may be considered as acting by one of three fundamental mechanisms.* (1) *Irritant cathartics* act by irritation of the intestinal tract and thus increase its motor activity. This leads to rapid propulsion of the intestinal contents. (2) *Bulk cathartics* increase the bulk of the intestinal contents until they exert more pressure on the mucous surface. They may increase the bulk by their ability to imbibe water and by their ability to resist digestion, e.g., agar; or by their ability to draw water to the intestine by the osmotic pressure which they exert, e.g., saline cathartics. (3) *Emollient cathartics* lubricate the intestinal tract and thus facilitate the passage of feces, e.g., liquid petrolatum. The line of demarcation between this classification is not always distinct; for example, the laxative effect of liquid petrolatum has been attributed to lubrication and to softening of the fecal mass. It has also been shown that it retains water in an emulsion and thus increases the bulk of the stool. This may be an important factor in the production of its effects.

To simplify classification the majority of the cathartics may be placed in two large groups, the *irritant cathartics* and those which produce cathartic action by increasing bulk or *bulk cathartics*. The following classification contains the more important cathartics.

Bulk Cathartics
Saline Cathartics
Plant Colloids
Emollient Cathartics
Irritant Cathartics
Anthraquinone (Emodin) Group
Resinous Group
Irritant Oils
Mercury Cathartics
Miscellaneous Cathartics
Phenolphthalein

BULK CATHARTICS

Saline Cathartics

Certain salts of sodium, potassium, and magnesium, which are not readily absorbed from the intestinal canal, act as cathartics by increasing the bulk, chiefly by "salt action." The contents of the intestines and the stools thus contain more fluid than usual. They act by hastening the passage of the contents through the small intestine so that a large volume of fluid enters the colon and produces purgation by distending it with fluid. They may also possess some specific stimulating action on the intestinal mucosa, thus increasing peristalsis.

The active constituent of the saline cathartics may be the anion which is very slowly absorbed by the intestine, while the cation may be rapidly absorbed. The cation of a salt, however, may also fail to be readily absorbed, as illustrated by magnesium chloride, while other chlorides may be rapidly absorbed. When both ions are slowly absorbed, as in

the case of magnesium sulfate, the cathartic action is very efficient. The chief saline cathartics used in medicine are:

Magnesium Sulfate.	Sodium Phosphate.
Solution of Magnesium Citrate.	Sodium Biphosphate.
Magnesia Magma.	Seidlitz Powders.
	Sodium Sulfate.

Pharmacological Action.—The *sulfates* pass through the tissues causing no injury, and are excreted unchanged. They may be reduced, under certain conditions of fermentation, to the sulfides. *Phosphates* are inactive and are excreted as phosphates by the kidneys. They increase the acidity of the urine.

The saline cathartics in therapeutic doses do not induce irritation of the intestines as do the vegetable cathartics. Their characteristic effect is retarded absorption produced by the presence of a concentrated amount of salt which tends to hold the water, permitting slow absorption by the gut.

A solution of isotonic sodium chloride is rapidly absorbed by the stomach and small intestine, but an isotonic solution of sodium sulfate is slowly absorbed, as it passes to the large bowel and on down toward the rectum. The weight of this volume induces increased peristalsis and aids evacuation.

With a hypotonic solution of sodium sulfate more fluid is absorbed and less reaches the large intestine, but a greater volume reaches the large intestine than with a smaller amount of sodium chloride. With a hypertonic solution of sodium sulfate, fluid is drawn to the bowel from the blood because of its higher osmotic pressure. The action results in the blood's giving up its fluid until the intestinal fluid is isotonic, then some absorption is possible.

These salts depend on fluid from the blood and tissues. In edema and dropsy the hypertonic saline cathartics drain the excess fluid from the blood into the bowel. This drainage of fluid from the blood tends to cause blood concentration and leads to a sensation of thirst and to lessened excretion of fluid by the kidney. Some salt is absorbed from the intestine, which also attracts water, and with dilute salts the blood becomes less concentrated and diuresis follows. Stronger solutions at first cause concentration of the blood and afterwards the excess of the salt in the blood causes diuresis.

Magnesium Sulfate is the most powerful and widely used saline cathartic. It is efficient in action, rarely causes discomfort, and has few side reactions. The principal disadvantage is an unpleasant taste. A 15 gram dose given in fruit juice is very effective. It does not irritate the intestine, is absorbed slowly, and the osmotic pressure of the salt prevents the absorption of fluid after the salt has been concentrated to a solution isotonic with the body fluids.

As a purgative:

℞

Magnesium Sulfate	30.00 Gm.	(℥j)
Ginger Syrup	15.00 cc.	(f℥ss)
Distilled Water q.s. ad	60.00 cc.	(f℥ij)

M. Sig.: Tablespoonful in glass of water every four hours as required.

Magnesium Citrate Solution is a flavored, carbonated, saline cathartic and is more expensive per dose than most of the other cathartics. It is exceedingly nauseating to many people and not infrequently causes violent purging.

Magnesia Magma is very palatable and easy to administer to children. Its alkalinity makes it desirable in hyperacidity. The addition of fruit juice converts it in part into magnesium citrate, which is more active. Its continued use may cause a sensation of burning in the rectal region.

Sodium Phosphate is used extensively in some proprietary medicines. It is frequently prescribed in bulk, and the patient is instructed to use the powder dissolved in water. The effervescent sodium phosphate is very palatable.

Sodium Biphosphate is an excellent laxative and is frequently used to acidify urine. It is prescribed either alone, in powder or aqueous solution, or with other drugs. This drug is commonly used in acidifying urine preliminary to giving methenamine, the only drawback being the laxative effect of the biphosphate.

Compound Effervescent Powders (Seidlitz Powders).—The cathartic principle is the solution of potassium and sodium tartrate rendered effervescent by the liberation of carbon dioxide. Tartrates are not readily absorbed and hence are fairly good saline cathartics.

Sodium Sulfate is again coming into popularity. It is a valuable drug to follow the administration of anthelmintics or when it is desired to deplete the body fluid. One teaspoonful of this salt with an equal amount of potassium bitartrate, taken with fruit juice, constitutes a pleasant remedy.

As a laxative:

℞

Sodium Sulfate	30.00 Gm. (℥j)
Potassium Bitartrate	30.00 Gm. (℥j)

M. Sig.: Teaspoonful in glass of hot lemonade before breakfast.

Toxicology.—Most of the saline cathartics have a bitter taste, and may, in concentrated form, produce nausea. Dilute solutions cause no untoward symptoms other than a slight pain and griping. Polyuria may follow the administration of saline cathartics, and the urine may have an unusually high percentage of salts.

Therapeutic Uses.—Saline cathartics may be employed to secure rapid evacuation in many disorders. They are indicated in (1) acute constipation, (2) intestinal putrefaction, (3) to relieve edema or dropsy by removing excess fluids, (4) to reduce obesity, (5) to lessen milk secretion, and (6) to reduce intracerebral pressure.

In *acute constipation* magnesium citrate, magnesium sulfate, magnesia magma, and Seidlitz powders are very useful. The fluid stools, which result from their use, make them especially useful for patients with hemorrhoids, anal ulcers, and painful pelvic conditions.

In *intestinal putrefaction* the same salts are indicated but in larger doses. Some recommend magnesia and magnesium carbonate for removing intestinal putrefaction, for they, being quite insoluble, are less liable to purge. The saline cathartics are *contraindicated* in nervous persons, as they produce depression owing to loss of fluid. They should not be used routinely in febrile illness and in debilitated or elderly persons.

For the treatment of *edema*, magnesium sulfate is very effective. It is used in a large dose dissolved in water (1:1). This method at present is considered less effective than the use of purine derivatives.

The sulfates and tartrates are frequently used in a single large dose. Sodium phosphate, given in jelly or milk, is a good remedy for the treatment of children.

Preparations

Magnesium Sulfate, *Magnesii Sulfas,* U.S.P., B.P. (Epsom salt). $MgSO_4.7H_2O$. Small, colorless, odorless crystals, with a cooling, saline, bitter taste. Freely soluble in water (1:1). *Dosage:* 15 Gm. (4 drachms) in solution.

Magnesium Citrate Solution, *Liquor Magnesii Citratis,* U.S.P. Magnesium citrate corresponding to about 1.8 per cent of magnesium oxide. *Dosage:* 200 cc. (7 fluidounces).

Magnesia Magma, *Magma Magnesiae,* U.S.P. (Milk of Magnesia). A suspension of magnesium hydroxide (about 7.5%) in water, forming a thick, white liquid. *Dosage:* Antacid, 4 cc. (1 fluidrachm); laxative, 15 cc. (4 fluidrachms). *Mistura Magnesii Hydroxidi,* B.P., 4-16 ml. (60-240 min.).

Sodium Phosphate, *Sodii Phosphas,* U.S.P., $Na_2HPO_4.7\ H_2O$, representing about 53.5 per cent of the anhydrous salt. *Dosage:* 4 Gm. (1 drachm). (B.P. preparation—$Na_2HPO_4 \cdot 12H_2O$. *Dosage:* 2 to 12 Gm.).

Sodium Biphosphate, *Sodii Biphosphas,* U.S.P., $NaH_2PO_4.H_2O$. *Dosage:* 0.6 Gm. (10 grains).

Compound Effervescent Powders, *Pulveres Effervescentes Compositi,* U.S.P., B.P. (Seidlitz Powder). The blue paper contains sodium bicarbonate (2.5 Gm.) and potassium and sodium tartrate (7.5 Gm.). The white paper contains tartaric acid (2.2 Gm.). *Dosage:* The contents of a white and of a blue paper are dissolved separately in about two fluidounces of water, and the solutions mixed.

Sodium Sulfate, *Sodii Sulfas,* U.S.P., B.P. (Glauber's salt), $Na_2SO_4.10\ H_2O$. Colorless, odorless, efflorescent crystals, or a granular powder, having a bitter, saline taste. Freely soluble in water (1:1.5). *Dosage:* 15 Gm. (4 drachms).

Plant Colloids

A number of vegetable gums and mucilages have been introduced recently for their alleged value in chronic constipation. They include bassoran, karaya, and tragacanth gum preparations, e.g., metamucil.

This group of cathartics may prove more satisfactory than liquid petrolatum in the treatment of chronic constipation. It is important, however, to administer plenty of water; otherwise there may be a tendency to the formation of dry and hard feces.

Agar-agar is a dried mucilaginous substance (galactan) extracted from several varieties of seaweed. It is not digested but absorbs water, thus it adds to the bulk of the feces and serves to carry water along to the lower bowel. The action requires from five to seven days. It is often combined with cascara, emulsified with liquid petrolatum, or combined with phenolphthalein.

It is one of the most valuable agents in the therapy of constipation of the spastic type, as it provides bulk without the irritant qualities of cellulose, vegetables, or bran.

Psyllium seeds are the seeds of the plant *Plantago psyllium.* They have a mild laxative action similar to that of agar. The seeds are soaked before using.

Bran.—Roughage is best supplied in the form of fruits, vegetables, and bran. Bran has been used with indiscretion for several years and

has produced harmful results, but when used to supplement a concentrated diet, it has its proper place in the dietary regime. It is contraindicated in spastic constipation and in cases of partial stenosis.

PREPARATIONS

Agar, *Agar*, U.S.P., B.P. *Dosage:* 4 Gm. (1 drachm).
Plantago Seed, *Plantaginis Semen*, N.F. (Psyllium Seed). *Dosage:* 7.5 Gm. (1¾ drachms).

Emollient Cathartics

Emollient cathartics include olive oil and liquid petrolatum.

Olive Oil.—Olive oil is a fixed oil obtained from the ripe fruit of *Olea europaea*. It is a valuable cathartic in cases of chronic constipation. It is not completely absorbed and it softens and increases the bulk of the stool, thereby increasing peristalsis. It is also employed in many official preparations, in the treatment of tuberculosis, gall bladder diseases, hyperchlorhydria, etc. In chronic gall bladder disease olive oil is given at bed time; it tends to empty the gall bladder. In the treatment of hyperchlorhydria or peptic ulcer, olive oil is given for its demulcent action and to lessen the production of hydrochloric acid. It is palatable and not particularly objectionable.

For laxative action it may be administered on retiring, or in divided amounts two or three times during the day. Olive oil cannot be replaced by cottonseed oil, as in the process of refining, certain fatty acids are removed from cottonseed oil which renders it nonlaxative. Externally, it is used in the treatment of indurative and pruritic skin diseases.

PREPARATION

Olive Oil, *Oleum Olivae*, U.S.P., B.P. *Dosage:* 30 cc. (1 fluidounce).

Liquid Petrolatum.—Liquid petrolatum (mineral oil) is a mixture of liquid hydrocarbons from petrolatum. It has continued to hold a prominent place in the treatment of chronic constipation because of its harmless properties: It is indigestible, practically nonabsorbable, and incapable of undergoing bacterial decomposition. It is apparently emulsified in the gut, and this tends to increase the bulk, which in turn is followed by stimulation of the intestinal wall and an increase in peristalsis. When the oil becomes emulsified, it penetrates the intestinal contents, mechanically softening the feces. Recent evidence indicates that mineral oil does not necessarily coat the intestines, interfering with absorption and secretion, to any great extent.

Liquid petrolatum has been accused of causing deficiencies of the fat-soluble vitamins. It will dissolve carotene (provitamin A) from food and excrete it in the feces. However, natural vitamin A is almost quantitatively absorbed from the gut in the presence of mineral oil, hence the addition of adequate amounts of vitamin A to mineral oil should be of value in such conditions as chronic constipation, if mineral oil is taken over long periods of time.

The average dose is 1 drachm to 1 ounce (4 to 30 cc.), and it is best given at bedtime or before breakfast. It can be easily flavored. Any one of the following flavoring oils is satisfactory: clove oil, 10 drops to 500 cc. of mineral oil; almond oil, 15 drops to 500 cc. of mineral oil, or 15 drops of either peppermint or spearmint oil to 500 cc. of mineral oil. This drug is particularly valuable in such conditions as hemorrhoids and fissures, and those conditions in which the intestinal lumen is reduced in caliber.

PREPARATIONS

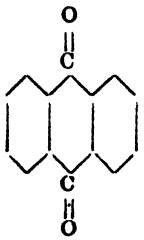
Liquid Petrolatum, *Petrolatum Liquidum*, U.S.P. *Dosage:* 15 cc. (4 fluidrachms). *Paraffinum Liquidum*, B.P.

Liquid Petrolatum Emulsion, *Emulsum Petrolati Liquidi*, U.S.P. Liquid petrolatum (50%), acacia, syrup, vanillin, alcohol, and distilled water. *Dosage:* 30 cc. (1 fluidounce).

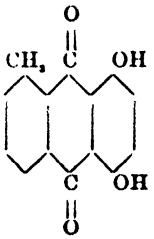
IRRITANT CATHARTICS

Anthraquinone or Emodin Group

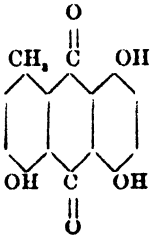
A number of drugs—rhubarb, senna, cascara, aloe, and their related compounds—are in themselves inactive, but when hydrolyzed or oxidized in the intestine they form various anthracene ($C_{14}H_{10}$) compounds. The slow liberation of these irritant substances produces catharsis. They act chiefly on the large intestine, since they are active only after hydrolysis. The most common of these substances are emodin and chrysophanic acid.



Anthraquinone ($C_{14}H_8O_2$)



Chrysophanic acid ($C_{15}H_{10}O_4$)



Emodin ($C_{15}H_{10}O_5$)

Emodin is partly absorbed in the urine, which is colored yellowish brown when it is acid, and red when alkaline. Some may be excreted in the milk and cause catharsis in the nursing baby. The pure principles of these drugs are not as satisfactory as the crude form, perhaps because they are absorbed too readily, producing toxic symptoms.

The anthracene group requires from eight to twelve hours to act; there is some griping which is attributed to the resinous bodies. Better results are secured by giving smaller doses at more frequent intervals. No marked tolerance is established by repeated doses. The anthraquinone cathartics tone up the muscles of the colon. They are particularly indicated for the treatment of chronic atonic constipation.

Rhubarb.—Rhubarb consists of the dried rhizome and roots of *Rheum officinale* and other species of Rheum. Its preparations are still used, but with decreasing frequency. Rhubarb is indigenous to China and was introduced to the Western World at about the beginning of the Christian Era.

Rhubarb contains a considerable amount of tannic acid as well as cathartic principles. The tannic acid acts as an astringent and tends to cause constipation after the bowel is emptied. Rhubarb may cause nausea, headache, and occasionally skin eruptions. Doses of 0.03 to 0.3 gram produce astringent action, and such doses are indicated in diarrhea; larger doses (1 to 5 Gm.) are indicated for laxative effects. Rhubarb and its extract are cathartic, bitter tonic, and stomachic, while

the aromatic syrup and tincture are laxative and slightly astringent. As cathartics they act chiefly on the colon and have a tendency to produce constipation after the initial laxative effect.

Rhubarb is still prescribed but usually as an adjuvant for other agents. Rhubarb preparations act in about eight hours, and they may be taken between meals or at night. Repeated use sometimes leads to the development of skin rashes. The taste is disagreeable; the drug frequently causes griping, and it often discolors urine.

For constipation:

℞

Rhubarb Powder
Magnesium Oxide
Sodium Bicarbonate ----------āā 30.00 Gm. (℥j)

M. Sig.: A teaspoonful two or three times daily when needed.

PREPARATIONS

Rhubarb, *Rheum*, U.S.P., B.P. Rhizome and root of certain species of Rheum. *Dosage:* 1 Gm. (15 grains).

Rhubarb Extract, *Extractum Rhei*, N.F. One gram of extract represents 2 Gm. of rhubarb. *Dosage:* 0.5 Gm. (7½ grains).

Aromatic Rhubarb Syrup, *Syrupus Rhei Aromaticus*, U.S.P. Aromatic rhubarb tincture (15%) and potassium carbonate in syrup. *Dosage:* 10 cc. (2½ fluidrachms).

Aromatic Rhubarb Tincture, *Tinctura Rhei Aromatica*, U.S.P. Rhubarb (20%), cinnamon, clove and myristica in glycerin, alcohol, and distilled water. Absolute alcohol content about 45 per cent. *Dosage:* 4 cc. (1 fluidrachm).

Senna.—Senna is the dried leaves of *Cassia Senna*, a plant indigenous to Africa and Arabia. It was used as a cathartic by the ancients. Senna is a popular domestic remedy. It may be administered by having the patient chew the leaves, but it is more frequently made into a tea. Senna belongs to the anthraquinone group of vegetable cathartics which act on the large intestine. It is one of the most valuable drugs of this class and is especially indicated for the treatment of chronic constipation. It is more active than Cascara Sagrada, and is more prone to cause griping and abdominal distress. It is contraindicated in any condition if there is intestinal inflammation present.

Senna is best prescribed in the form of a tea. To this may be added manna, which serves to sweeten it and increases its laxative effect. Senna taken in this form does not gripe. Compound Senna Powder, formerly known as Compound Licorice Powder, is prescribed alone or in fruit juice.

PREPARATIONS

Senna, *Senna*, U.S.P. (Senna Leaves). *Dosage:* 2 Gm. (30 grains).

Senna Fluidextract, *Fluidextractum Sennae*, U.S.P. Senna (100%). Absolute alcohol content about 25 per cent. *Dosage:* 2 cc. (30 minims). *Extractum Sennae Liquidum*, B.P. *Dosage:* 0.6-2 ml. (10-30 minims).

Compound Senna Powder, *Pulvis Sennae Compositus*, N.F. Senna (18%), washed sulfur (8%) with glycyrrhiza, oil of fennel and sugar. *Dosage:* 4 Gm. (1 drachm).

Senna Syrup, *Syrupus Sennae*, U.S.P., B.P. Senna Fluidextract (25%) and coriander oil in sucrose and water. Absolute alcohol content about 6 per cent. *Dosage:* 8 cc. (2 fluidrachms).

Aloe.—Aloe is the name given to the dried juice of several species of the cactuslike aloe plants of Arabia and East Africa. It contains the active principle aloin, a mixture of anthracene derivatives. Aloin is very bitter, therefore it must be administered in pills. Small doses may be used as a stomachic. Moderate doses are laxative and cause griping, and therefore are often combined with belladonna or carminatives. This drug is satisfactory for chronic constipation. The effects are similar to those of cascara, but it is somewhat more irritant. Aloe causes congestion of the pelvic organs and is therefore contraindicated in pregnancy, menstruation, and in the presence of hemorrhoids.

Aloin, obtained from aloe, is the most frequently used preparation. It is usually prescribed as Compound Laxative Pills or in some other combination of purgatives. The drugs apparently act on the lower part of the intestine. This drug is particularly useful for correcting the constipative effect of iron medication.

For chronic constipation:

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Aloe Pills ---------- No. XXX

Sig.: One pill at bedtime (N.F.).

PREPARATIONS

Aloe, *Aloe*, U.S.P., B.P. *Dosage:* 0.25 Gm. (4 grains) as pills.

Aloe Pills, *Pilulae Aloes*, N.F., B.P. Each pill contains aloe, 0.13 Gm. (2 grains) with soap. *Dosage:* 2 pills.

Aloin, *Aloinum*, U.S.P. Obtained from aloe. *Dosage:* 0.015 Gm. (¼ grain) in pills.

Aloin, Strychnine and Belladonna Pills, *Pilulae Aloini, Strychninae et Belladonnae*, N.F. Each pill contains aloin 0.013 Gm. (⅕ grain), strychnine, 1 mg. (1/60 grain), and pilular belladonna extract, 0.008 Gm. (⅛ grain) with glycyrrhiza and glucose. *Dosage:* 1 pill.

Cascara Sagrada.—Cascara sagrada is obtained from the bark of a shrub, *Rhamnus purshiana*, found on the Western Coast of the United States. Cascara sagrada as now marketed is effective and causes little discomfort. As is the case with this entire group of drugs, the active cathartic principles are liberated only after hydrolysis in the alkaline lower third of the small intestine. The cathartic action is exerted almost entirely upon the large bowel. The effect is produced in from eight to twelve hours. It produces its effect by irritation, but usually without griping pains, and the irritation is not severe. Since its efficiency is not lost by repeated use, it is an effective drug in chronic constipation. The extract is sometimes used, but the fluidextract or the aromatic fluidextract of the drug is chiefly employed. The aromatic fluidextract is not as active as might be expected, because some of the bitter principles are removed. The simple fluidextract is very bitter, so if given three times a day it also exercises a tonic effect.

These preparations are prescribed alone or with milk, or small amounts may be added to other formulas to make them laxative. Cascara sagrada is a stimulant, laxative, and cathartic, and is used chiefly in chronic constipation. It softens the stools with little irritation. No tolerance is developed. A dose of 15 drops of the fluidextract, three times daily, is satisfactory. As a tonic and laxative:

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Cascara Sagrada Fluidextract ---- 30.00 cc. (f℥j)
Glycerin
Aromatic Elixir ---------- āā 15.00 cc. (f℥ss)
M. Sig.: Teaspoonful after meals.

PREPARATIONS

Cascara Sagrada, *Cascara Sagrada*, U.S.P., B.P. *Dosage:* 1 Gm. (15 grains).

Cascara Sagrada Extract, *Extractum Cascarae Sagradae*, U.S.P. One gram of extract represents 3 Gm. of cascara sagrada. *Dosage:* 0.3 Gm. (5 grains). Cascara Sagrada Extract Solution, *Extractum Cascarae Sagradae Liquidum*, B.P., ½-1 fl. dr.(2-4 ml.).

Cascara Sagrada Extract Tablets, *Tabellae Cascarae Sagradae Extracti*, U.S.P. *Dosage:* 0.3 Gm. (5 grains).

Cascara Sagrada Fluidextract, *Fluidextractum Cascarae Sagradae*, U.S.P. Cascara sagrada (100%). Absolute alcohol content about 18 per cent. *Dosage:* 1 cc. (15 minims).

Aromatic Cascara Sagrada Fluidextract, *Fluidextractum Cascarae Sagradae Aromaticum*, U.S.P. Absolute alcohol content about 18 per cent. *Dosage:* 2 cc. (30 minims). *Elixir Cascarae Sagradae*, B.P., 2-4 ml. (30-60 min.).

Resinous Group

The cathartic resins include jalap, ipomoea, elaterin, colocynth, and podophyllum. These substances are rarely used now due to their drastic action. Only podophyllum will be discussed.

Podophyllum.—Podophyllum is the dried rhizome and roots of the perennial herb *Podophyllum peltatum* which grows in Canada and in the United States. It was early adopted by the settlers for general use. Its active principles are resins. Podophyllum is cholagogue, laxative, and cathartic, and is used in chronic constipation. Because it acts slowly, producing soft stools in from twelve to thirty-six hours, podophyllum is a valuable laxative in chronic constipation. As its effects are somewhat uncertain, it is advisable to begin with a smaller dose than that recommended by the N.F., and increase it if necessary. The resin of podophyllum, which is the preparation used, is very irritating to the eye and mucous membranes in general. It is usually ordered in small doses with other drugs to increase its purgative action.

PREPARATIONS

Podophyllum, *Podophyllum*, N.F. Yields not less than 5 per cent of resin.

Podophyllum Resin, *Resina Podophylli*, N.F. *Dosage:* 0.01 Gm. (⅙ grain). Podophylli Resina, B.P., ¼-1 gr.

Irritant Oils

The irritant oils include castor oil and croton oil. Due to its violent irritant action the latter is rarely used in medicine.

Castor Oil.—Castor oil is a fixed oil obtained from the seed *Ricinus communis*. The highly refined oil that may now be purchased is odorless and almost tasteless.

Castor oil consists chiefly of the triglyceride of an unsaturated fatty acid, ricinoleic acid. The neutral fat is active only when saponified

in the intestine. The cathartic action is due to motor stimulation of the small intestine. The internal secretion is not increased, the fluid stools being due chiefly to the rapid passage of the feces. Passage may occur in two hours instead of a normal eight-hour period.

Castor oil is the most valuable and extensively used purgative in medicine. It is characterized by efficient purgative action followed by a tendency to check intestinal activity. This is desirable in the treatment of diarrhea, dysentery, and other digestive disturbances. It is particularly valuable in the treatment of diarrhea caused by irritants and infections, and is also valuable in securing the rapid removal of toxic drugs from the gastrointestinal tract.

The drug is best administered before breakfast on an empty stomach. It may be given in lemon juice, ginger ale, or in various other ways. The usual dose is ½ to 1 ounce. In administering the oil to children, the first dose is frequently vomited. If repeated promptly, it will almost always be retained.

In *diarrhea* or *dysentery* a desirable mixture is 1 fluidrachm (4 cc.) of paregoric and 1 fluidounce (30 cc.) of castor oil, beaten up into a creamy mixture and administered alone. Castor oil often has a constipating effect after purgation, so that it may be advisable to follow it with some other laxative. If it is used continuously, gastric symptoms may occur.

Externally, it is used in the treatment of *burns*, *ulcers*, and chronic indurative *skin diseases*.

PREPARATION

Castor Oil, *Oleum Ricini*, U.S.P., B.P. *Dosage:* 15 cc. (4 fluidrachms).

Mercurial Cathartics

While mercury is a general protoplasmic poison, several of the insoluble mercury salts are slightly soluble in alkaline secretions of the intestines and produce a mild irritation followed by catharsis.

Mode of Action.—Preparations of mercury pass through the stomach unchanged and apparently form some mercury-protein combinations in the intestine. The compounds thus formed are quite active, and it is thought that the union with the intestinal protein causes the *increased peristalsis*, *increased glandular secretions*, and *decreased absorption*. The contents of the small intestine pass more rapidly to the large intestine.

Calomel (mild mercurous chloride), and *mercury with chalk* are preparations used for their cathartic action. *Mild mercurous chloride* (calomel) produces a dark green semisolid stool in ten to twelve hours. The action is very mild and is rarely contraindicated even in enteritis. This compound also produces an antiseptic action in the intestines, reflected by the decrease of urinary indoxyl. Larger doses may favor bacterial growth by diminishing intestinal resistance. Calomel is contraindicated in conditions in which there is a possibility of intestinal obstruction, as it is slowly absorbed and may produce mercury poisoning. Calomel produces a marked diuresis in cases of edema but does not produce diuresis in normal persons. At one time calomel was very popular but it is now rapidly falling into disuse.

To a large extent the popularity of mercury with chalk is waning. *Mercury with chalk*, or gray powder, is used chiefly for infants, since it has a milder action than calomel.

For adults, the mild mercurous chloride is the preparation of choice. It may be administered with sugar, in powder or in capsules. It is often

combined with some other purgative, as phenolphthalein, podophyllin, rhubarb, etc., and administered in capsules.

A very satisfactory plan for administering calomel is to give it in small doses ($\frac{1}{10}$ grain capsules) and repeat every twenty minutes until one or two grains have been given.

In addition to its use as a cathartic, calomel is also used as a diuretic, as an antiseptic, and in the treatment of syphilis.

Contraindications.—Mercury is contraindicated in weakness, anemia, and cachexia. In severe nephritis, weak digestion, and advanced tuberculosis of the lungs mercury should be used with extreme caution. The use of mercury is not contraindicated in pregnancy; in fact, clinical results have shown that in patients with syphilis mercury diminished the tendency to miscarriage. Other contraindications are scurvy, dysentery, severe heart disease, disease of the gums, and in cases in which iodides have been administered internally.

As a purge:

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Mild Mercurous Chloride
Phenolphthalein
Rhubarb Powder ---------- āā 0.30 Gm. (gr.v)
Mix and put into 3 capsules.
Sig.: Take one each hour.

PREPARATIONS

Mercury with Chalk, *Hydrargyrum cum Creta*, N.F. (Gray Powder). Mercury (about 38%), with prepared chalk (57%), honey, and water. *Dosage:* 0.25 Gm. (4 grains).

Mild Mercurous Chloride, *Hydrargyri Chloridum Mite*, U.S.P. (Calomel). *Hydrargyri Subchloridum*, B.P *Dosage:* Laxative, 0.12 Gm. (2 grains).

Mild Mercurous Chloride Tablets, *Tabellae Hydrargyri Chloridi Mitis*, N.F. (Calomel Tablets). Contains 92.5 to 107.5 per cent of the stated amounts of Mild Mercurous Chloride. *Dosage:* 0.06 Gm. (1 grain) of Mild Mercurous Chloride.

Miscellaneous Cathartics

Phenolphthalein.—Phenolphthalein, a condensation product of phenol and phthalic anhydride, is used in medicine chiefly as a cathartic. It is a white powder almost insoluble in water but soluble in alcohol (1:13). Its derivative, *phenolsulfonphthalein*, is used in testing kidney function.

Pharmacological Action.—Phenolphthalein resembles the anthracene purgatives in its general *mode of action*. Berk et al. (1942) believe phenolphthalein acts directly on the muscle.

Part of the drug is absorbed and is *excreted* in the bile, and hence will produce purgative effects for three or four days. After oral administration 85 per cent appear in the feces while traces are found in the urine. After hypodermic administration it is excreted in the urine, feces, saliva, and tears.

Toxicology.—Phenolphthalein has a cumulative action if taken regularly. The chief toxic effects produced are skin rashes and occasionally renal irritation. Large overdosage can produce severe intoxication, and hence it is unwise to dispense for use by children in the form of chocolate tablets.

Therapeutic Uses.—The use of phenolphthalein should be supervised and stopped when toxic manifestations develop. It is useful in the treatment of chronic atonic constipation and is considered a fairly safe and reliable cathartic. In spastic constipation its use is contraindicated.

PREPARATION

Phenolphthalein, *Phenolphthaleinum*, U.S.P., B.P. *Dosage:* 0.06 Gm. (1 grain).

CHOICE OF CATHARTIC

The choice of a cathartic, when one is indicated, is an important detail with reference to the success of the treatment. The following points should be kept in mind:

1. Cascara sagrada is a drug especially indicated for constant daily use when a mild, effective cathartic is desired. It produces no tolerance, and decreasing doses are possible. It may be used in conjunction with mineral oil.

2. Castor oil is recommended for an occasional powerful purge. It is mildly irritating to both the small and the large intestine.

3. Mild mercurous chloride (calomel) may be given by mouth in the presence of nausea and vomiting, as it is not offensive to the stomach. Care should be exercised, as mercurial poisoning may occur.

4. Phenolphthalein has no great advantage over other cathartics other than the ease of administration. The drug occasionally gives rise to a permanent hemorrhagic rash.

5. Saline cathartics. The milder salines are the only ones that should be used habitually. Magnesium oxide and Seidlitz powders are pleasant ways of administering mild cathartics.

6. The use of cathartic pills should be discouraged, for a regular habit may soon be established.

7. Agar is a valuable therapeutic agent for the spastic type of constipation. It provides the desired bulk and lacks the irritating properties of cellulose and bran. It may be given with mineral oil or cascara. The agar mineral emulsions, so widely advertised, are of little value because of the small amount of agar (2 to 6%) present. The laxative effect of these emulsions is usually due to the presence of phenolphthalein or magnesium.

Prescribe Cathartics Cautiously.—Cathartics are not, as yet, included among the dangerous drugs, but they are prescribed carelessly and taken light-heartedly by physicians and laymen alike. Under certain conditions, however, a cathartic can produce grave results. A cathartic at the beginning of an acute illness tends to dehydrate an already dehydrated patient, depleting the fluid reserves still further. Cathartics should never be given in diseases in which diarrhea is a symptom; and only in the early stages of an acute abdominal infection is the administration of a cathartic indicated.

According to Fantus (1939) "even the mildest and blandest laxative, as well as enemas, must be charged with a tendency to get the bowel into sluggish habits, for this very ease with which solid or liquid contents pass along the bowel diminishes the necessity for muscular effort and adds to atony and ultimately to atrophy."

Routine administration of cathartics before surgical operations only disturbs the water balance of the tissues and in most cases encourages shock. Purgation is exhausting and in conditions such as

lobar pneumonia hinders the chances of recovery. *The use of cathartics as a routine procedure in any branch of therapeutics is poor treatment.*

References

Alvarez, W. C.: Gastro-Enterology, New York, 1949, Paul B. Hoeber, Inc.

Bethea, O. W.: Use and Abuse of Purgatives, Internat. M. Digest. 24: 239-245, 1934.

Carlson, A. J.: The Secretion of Gastric Juice in Health and Disease, Physiol. Rev. 3: 1, 1923.

Collins, E. N.: Use of Aluminum Hydroxide and Other Nonabsorbable Antacids in the Treatment of Peptic Ulcer, J. A. M. A. 127: 899, 1945.

Emery, E. S.: The Use of Adsorbents in the Gastro-Intestinal Diseases, J. A. M. A. 108: 202, Jan. 16, 1937.

Fantus, B.: Technic of Medication, Chicago, 1939, American Medical Association.

Friedenwald, J., and Morrison, S.: Use of Gastric Antacids, J. A. M. A. 108: 879, Mar. 13, 1937.

Gray, H., and Tainter, M. L.: Colloid Laxatives Available for Clinical Use, Am. J. Digest. Dis. 8: 130, 1941.

Guides to Therapy for Medical Officers, Washington, D. C., 1942, U. S. Government Printing Office.

Handbook of Therapy, Chicago, 1937, American Medical Association.

Hirschman, L. J.: Synopsis of Ano-Rectal Diseases, St. Louis, 1942, The C. V. Mosby Co.

Morgan, J. W.: The Harmful Effects of Mineral Oil Purgatives, J. A. M. A. 117: 1335, 1941.

Nelson, E. E.: The Treatment of Constipation, Internat. M. Digest. 42: 308, 1943.

Vaughan, W. T.: The Diagnostic Program in Food Allergy, "Food Diary," Diarrhea, Am. J. M. Sc. 182: 459, Oct., 1931.

Willard, J. H.: Digestive Diseases in General Practice, Philadelphia, 1942, F. A. Davis Co.

CHAPTER VII

ANTISEPTICS, DISINFECTANTS, AND ANTI-INFECTIVES

I. ANTISEPTICS AND DISINFECTANTS

"In Nature's battle against disease the physician is but the helper who furnishes Nature with weapons, the apothecary is but the smith who forges them."

—Paracelsus (1493-1541).

Probably no man has exerted a greater influence on the practice of surgery than Joseph Lister. He was greatly influenced by an article telling of the work of Pasteur who had shown that "the air was full of living germs and that these were carried on particles of dust floating on the atmosphere; that the activity of these particles of dust can be destroyed by heat, and that they can be filtered off by cotton wool." It occurred to Lister that suppuration in wounds could be prevented "by applying in a dressing some material capable of destroying the life of the floating particles."

Lister, who was interested in the treatment of compound fractures, used cotton soaked in carbolic acid as a dressing for these fractures. He tried out various dilutions of phenol for washing skin preparatory to operating. Later he used carbolized cerate and also oil of eucalyptus. In 1870 he introduced the carbolic acid spray, in the belief that it would destroy germs before they came in contact with the field of operation. Later, many other drugs were proved more valuable than phenol because of their less destructive action on tissues. Now surgeons try to work under strict aseptic conditions and use a wide variety of antiseptics and disinfectants to cleanse the skin, hands, and instruments.

Preventive medicine and surgery are both dependent upon efficient medicinal agents for the prevention and treatment of infections. Those drugs commonly used are termed "antiseptics," and "disinfectants." The most acceptable definitions are:

Antiseptic.—"A substance that opposes sepsis, putrefaction or decay." The United States Food and Drug Administration has recognized that the word "antiseptic" has two meanings—to kill bacteria or to prevent their growth, depending upon the use of the product. Products, such as salves, ointments, etc., may be properly designated as antiseptics, if they inhibit the growth of bacteria. Mouthwashes, douches, gargles, etc., may be designated as antiseptics, however, only if they destroy bacteria in the dilutions recommended and in a period of time compatible with their usage.

Disinfectant.—"An agent that frees from infection." It is usually a chemical agent that destroys bacteria. It is synonymous with germicide and bactericide.

Mode of Action of Antiseptics.—The ideal antiseptic is one that will actively inhibit the growth of bacteria in the presence of body fluids without injuring the cells of the host. In view of the great similarity between bacteria and the cells of the host the problems involved in

securing agents with specific bacteria action is most difficult. There is some information available regarding the effects of antiseptics on bacteria, but experimental difficulties make it hard to determine the interactions of antiseptics with tissue cells.

The following reactions are believed to take place between antiseptics and bacteria.

1. NEUTRALIZATION OF FREE BASIC OR ACIDIC GROUPS of the bacterial protein. Such neutralization of vital functional groups seems to cause metabolic disturbances in the microorganisms, and eventually death.

2. FORMATION OF NONIONIZED COMPLEXES between antiseptics and bacteria may explain the antiseptic activity of some compounds. Anionic antiseptics have been proposed for certain neutral or faintly alkaline sodium salts of acids of high molecular weight, familiar examples being acid fuchsin (acid dyes), ammonium and calcium mandelates, and common soap. These antiseptics may function through the interaction of their acidic ions with the basic groups of bacteria to form feebly ionized compounds (Stearn and Stearn, 1924).

The cationic antiseptics, which are the converse of the anionic group, consist of neutral salts of bases of high molecular weight and include the "basic dyes," such as brilliant green and crystal violet, triphenylmethane dyes, and the acridine antiseptics (proflavine, acriflavine), as well as colorless higher aliphatic amines represented by zephiran. This group is thought to act by uniting with the acidic group in bacteria to form feebly ionized compounds.

3. SURFACE ACTIVITY of certain drugs may explain their antibacterial action. The property of surface activity, that of congregating at a boundary, is due to the molecule possessing a powerful polar group, such as —COOH or —NH_2 at one end of the molecule while the rest of the molecule constitutes the "nonpolar" group. In general the polar groups are brought together while the nonpolar groups attract each other. This mechanism could concentrate substances of an antibacterial nature on or in the cell wall and thus cause destruction of the cell.

4. FORMATION OF COMPLEXES.—Formaldehyde appears to act by forming complexes involving the free amino groups of protein. No other aldehyde, however, has comparable antiseptic properties.

5. HALOGENATING ACTION.—The halogenating agents, iodine, and organic compounds liberating hypochlorous acid, appear to act both by halogenating free amino groups and through direct oxidizing action.

6. OXIDIZING ACTION.—Agents such as ozone, hydrogen peroxide, and permanganates are bactericidal because of their frank oxidizing action. These agents are rapidly inactivated by bacteria and human tissues and do not distinguish between bacteria and human tissues.

7. DISPLACING OF ESSENTIAL METABOLITE.—The sulfonamides lack general antiseptic activity except in high concentration. Their mode of action is thought to be due to their ability to displace an essential metabolite, apparently *p*-amino-benzoic acid, from a bacterial enzyme.

Selection of a Disinfectant.—In general, the selection of a disinfectant for the sterilization of gloves, clothing, and instruments, is relatively easy and is limited only to the susceptibility to damage from the agents used, the amount of labor and the disinfectants available. The disinfection of tissues, however, is a matter of great importance. Naturally the necessity of disinfection must be carefully weighed against the possible damage of the agent to the tissues involved.

Efficiency of Disinfectants.—The efficiency of disinfectants depends on many factors. Some of these factors are: (1) concentration of disinfecting agent; (2) the ability to penetrate and diffuse into tissues; (3) length of time agent is in contact with microorganisms; (4) the temperature at which agents are applied; (5) the reaction of the environment; (6) the number and type of organisms present and the type of environment (media) in which they are found.

The measurement of the relative efficiency of various disinfectants is of considerable importance and a number of methods for testing the potency of disinfectants have been devised. The best known is the Rideal-Walker method or some modification of it. The *phenol coefficient* in the Rideal-Walker method is determined by dividing the figure indicating the degree of dilution of an antiseptic that will kill *Bacillus typhosus* in a given time by the degree of dilution of phenol that will produce the same results in the same time under identical conditions. The phenol coefficient is valuable only for the disinfectants related to phenol, and is of little value for metals, iodine, chlorine, and other antiseptics.

A vast array of chemical compounds and proprietary preparations, many of which are exploited with exaggerated claims, are available. Only a few of the most important substances will be discussed.

PHENOL AND DERIVATIVES

Phenol

Phenol, carbolic acid (C_6H_5OH), a monohydroxy benzene, is obtained from coal tar by fractional distillation or made synthetically. It appears as colorless or reddish crystals which are soluble in water (1:15), alcohol, glycerin, and oils. Solutions in fatty oils are not antiseptic because their affinity for the fatty oils is so great that they exert little effect on bacteria or tissues.

Phenol was the first of the modern antiseptics to be used, being introduced by Lister in 1867. It was used extensively as an antiseptic following its introduction but is seldom used for this purpose today. Lister's confidence in phenol so firmly established the reputation of this compound that it has become the standard by which germicidal powers of antiseptic and disinfectant compounds are compared.

Pharmacological Action.—Phenol possesses antiseptic and germicidal action; also local anesthetic and caustic action. Aside from its local action phenol produces marked changes in the central nervous system.

Phenol is rapidly *absorbed* from the stomach, intestines, skin, and mucous membranes. After absorption a large portion is oxidized to hydroquinone and pyrocatechin which are *excreted* in the urine, giving it a brown color. Some of the drug is combined with glycuronic acid and some is combined with sulfuric acid to form phenyl-sulfuric acid, both of which are excreted in the urine. The formation of these many compounds with phenol is a striking example of the many ways a drug is acted upon in the body.

Antiseptic Action.—Phenol possesses the characteristic properties of the phenol derivatives; some of its derivatives are superior, however, at least for some purposes. It is generally thought that phenols react with bacterial proteins to form insoluble albuminates and that their disinfectant action is due to their ability to denature proteins.

Phenol is poisonous to protozoa, plant cells, spermatozoa, and practically all unicellular organisms. It shows, however, no marked specificity on any particular species of bacteria, although it destroys delicate organisms, such as *B. typhosus*, with considerable ease. Tubercle bacilli are killed by exposure to 5 per cent phenol for twenty-four hours. Phenol is little used today because it kills tissue cells almost as readily as it kills bacteria. Furthermore, it is toxic when taken internally and hence is unsafe as a general disinfectant for public use.

Local Action.—Phenol causes coagulation of proteins when brought in contact with tissues. A 5 per cent solution will cause tingling and warmth in the fingers followed by shrinking of the skin. This action is accompanied by mild anesthetic and analgesic action; an action made use of in compounding antipruritic lotions or ointments. Solutions of phenol, when used as wet dressings, often penetrate and destroy tissues. Weak solutions are even more dangerous, for they give no danger signal of their destructive action as a stronger solution would. Mucous membranes become irritated and necrotic when phenol is applied.

Central Action.—Small doses of phenol produce fleeting analgesic and antipyretic actions, followed by pronounced toxic symptoms of such a nature that it cannot be used in therapeutics. Large doses produce collapse and coma.

Action on Circulation.—Small doses intravenously cause marked fall in blood pressure, caused apparently by cardiac and vasomotor action. Large doses slow the heart due to direct cardiac action. When given orally the fall of blood pressure is prolonged because of continuous absorption.

Other Actions.—Respiration becomes slow and shallow following phenol administration. *Temperature* falls due to collapse and alteration of the heat center. *Secretions*, especially saliva, sweat, and tears, are increased by phenol.

Toxicology.—Large quantities of phenol are occasionally taken orally either by accident, or with suicidal intent. Phenol is readily absorbed from wounds and mucous membranes, hence poisoning may follow its use as a wash for large areas. Orally, phenol causes a burning pain in the mouth, pharynx, and stomach. It is quickly absorbed and produces immediate collapse with intense and striking cyanosis. In less severe cases, rapid pulse, cold perspiration, and the typical picture of shock are characteristic. There occasionally occurs twitching of the muscles of the face and limbs. Convulsions are rare. Death occurs from respiratory paralysis. The *fatal dose* varies with route of administration. Introduction by routes other than the alimentary canal, such as by the vaginal route, may require but small quantities to produce death. A *dose* of 1 to 20 grams may cause death in a few minutes or usually in less than twenty-four hours.

Post-mortem Appearances.—Phenol corrodes the tissues with which it comes in contact, producing a white appearance, but after prolonged contact, red patches appear. The urine is dark green in prolonged cases. The blood is usually dark and fluid; the brain, liver, and lungs are congested.

Treat phenol poisoning by stomach lavage with liquid petrolatum (250 cc.), followed by potassium permanganate. The use of alcohol, which is commonly recommended in textbooks, is contraindicated. Alcohol dissolves phenol rapidly but as alcohol is quickly absorbed, phenol is carried immediately into the system.

If stomach tube is not available, inject 0.006 Gm. (1/10 grain) apomorphine hydrochloride. Inject intravenously 1000 cc. of 5 per cent

glucose in physiological saline. Provide inhalation of 10 per cent carbon dioxide and 90 per cent oxygen or apply artificial respiration if necessary. Wash off surface burns with 95 per cent alcohol.

Therapeutic Uses.—Phenol is used chiefly as an antiseptic and germicide and in ointments or solutions for its anesthetic and antipruritic action. As a solid, phenol is used in ointments, oily liquids, etc., while liquefied phenol is usually used for the preparation of solutions.

Skin Diseases.—Phenol acts as a local anesthetic. In consequence it is employed to relieve itching in the treatment of eczema, urticaria, dermatitis, etc. Solutions or ointments of from 0.5 to 2 per cent are recommended. In treatment of pruritus:

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Phenol Menthol ----------āā	1.3 Gm.	(gr.xx)
Petrolatum ----------q.s. ad	30.0 Gm.	(℥j)

Mix and stir well.
Sig.: Apply locally.

For toothache:

℞

Phenol ----------	0.70 Gm.	(gr.xj)
Chloroform ----------	12.00 cc.	(f℥iij)
Clove Oil ----------q.s. ad	30.00 cc.	(f℥j)

M. Sig.: One drop on tooth.

As Antiseptic and Disinfectant.—Five per cent solutions are used for the disinfection of utensils, instruments, the hands, etc. Phenol has been used as an antiseptic in *mouthwashes, gargles,* and *lotions* in 0.5 to 1 per cent strengths. Injections of approximately 0.5 to 0.8 cc. of a 10 per cent solution are recommended to *abort boils.* Phenol, full strength, may be used to *cauterize* chancroids, venereal warts, and ulcers. *Earache,* resulting from congestion of the tympanic membrane, is frequently relieved by the use of a 3 to 5 per cent solution of phenol in glycerin. Inhalations have been advocated in conditions such as *pulmonary gangrene.* It is useless as an antiseptic in stomach fermentation. In the treatment of *internal hemorrhoids* 5 per cent phenol in almond oil or compressed cottonseed oil is a popular and effective preparation. Sutton recommends that a saturated solution of sodium sulfate, with 0.5 per cent phenol, be used for *ivy poisoning.*

PREPARATIONS

Phenol, *Phenol,* U.S.P., B.P. Colorless crystals or white crystalline masses, sometimes becoming reddish with a characteristic odor.

Liquefied Phenol, *Phenol Liquefactum,* U.S.P., B.P. Phenol liquefied by about 10 per cent of water.

Phenol Ointment, *Unguentum Phenolis,* U.S.P. Phenol (2%), glycerin (2%) and white ointment (96%). (B.P., 3 per cent in ointment base.)

Cresols

Cresols are methyl phenols ($C_6H_4CH_3OH$) obtained by the introduction of alkyl groups into phenol, or manufactured by fractional distillation from coal tar or phenol "crude carbolic acid." They are more important than phenol from the standpoint of practical disinfection.

Pharmacological Action.—The three cresols, *ortho-*, *meta-*, *para-*cresol, resemble phenol closely in action, are moderately soluble in water (1:50), and readily form emulsions in the presence of soaps or alkalies. Of the three isomers, the *meta-* form is the most antiseptic and least toxic, and the *para-* the most toxic. The introduction of the methyl group increases the germicidal efficiency while the toxicity is not increased, at least in the same ratio. The symptoms and treatment of cresol poisoning are as for phenol.

Another advantage of the cresols over phenol is their lower cost. However, they have certain disadvantages, such as a disagreeable odor, which is due mainly to impurities, their limited solubility in water, and their variability in composition. The cresols may be rendered soluble by the addition of soap.

The toxicity and local actions of the cresols, as of other phenols, may be diminished by "masking" the active OH group through replacement of the H by acid radicals. Thus, $CH_3C_6H_4O(CH_3CO)$, the acetic acid ester of metacresol, $CH_3C_6H_4OH$, is said to possess antiseptic and analgesic properties, and is apparently free from toxic effects.

Therapeutic Uses.—Cresol is used in medicine solely for its disinfectant properties. The saponated solution is used almost exclusively. It is employed chiefly as a *surgical antiseptic*, both for sterilizing instruments (3-5 per cent Saponated Cresol Solution) and as a wound dressing in 1 per cent concentration. The diluted solution (1-5 per cent) is used for the disinfection of the skin, for vaginal douches, and for sterilizing and lubricating the hands.

The *acetic acid ester of metacresol*, $CH_3C_6H_4O(CH_3CO)$, is recommended in the treatment of affections of the nose, throat, and ear, such as follicular tonsillitis, nasal suppuration, furunculosis, and purulent otitis media. It is said to be nontoxic to mucous membranes. Use in pure form or in dilution with oils or alcohol by direct application or spray.

PREPARATIONS

Cresol, *Cresol*, U.S.P., B.P. A mixture of isomeric cresols obtained from coal tar. *Dosage:* 0.06 cc. (1 minim).

Saponated Cresol Solution, *Liquor Cresolis Saponatus*, U.S.P. Cresol (50%) with vegetable oil, potassium hydroxide and distilled water (B.P., solution of cresol with soap).

Creosote and Guaiacol

Creosote, which is obtained from the destructive distillation of wood, is a complex mixture composed chiefly of *guaiacol* and *cresol*, and is used to a limited extent in medicine as an expectorant and germicide.

Action and Uses.—Opinions vary as to the germicidal power of creosote. Its phenol coefficient is approximately 3.6. It is strongly antiseptic and antipyretic, and slightly less irritant and toxic than phenol.

Creosote and guaiacol were extensively employed in tuberculosis and chronic bronchitis, with doubtful clinical value. For these purposes Creosote, *Creosotum*, N.F., B.P.; Creosote Carbonate, *Creosoti Carbonas*, N.F.; and Guaiacol, *Guaiacol*, N.F., B.P., are used.

Trinitrophenol

Trinitrophenol, picric acid, $C_6H_2(NO_2)_3.OH$, is a yellow, crystalline, odorless substance with a bitter taste. It is sparingly soluble in water (1:78) and soluble in alcohol (1:12).

Action and Uses.—Picric acid is used as a dye, a test and a fixing agent, as an explosive, and in medicine as an *antiseptic, anthelmintic,* and for *treating burns.* It possesses antiseptic, germicide, and local anesthetic action. The use of this drug is confined chiefly to the preparation of wet dressings for the treatment of burns, and to render the skin sterile before operations. In the treatment of superficial wounds and eczemas, use is made of its anesthetic, antiseptic, astringent, and stimulating action. Internally it is highly toxic, producing nausea, vomiting, and diarrhea, and stains the skin and mucous membranes a yellow color resembling jaundice. Toxic absorption may occur from its application to extensive denuded areas. *Treatment* consists of gastric lavage followed by ingestion of large amounts of water to aid elimination. The white of an egg is considered a valuable antidote. The stains can be removed with potassium sulfate powder.

PREPARATION

Trinitrophenol, *Trinitrophenol,* N.F., B.P. (Picric Acid). "Trinitrophenol explodes when heated rapidly or when subjected to percussion."

MERCURY AND MERCURY DERIVATIVES

Since the time of the alchemists, mercury has been regarded as a drug capable of curing many diseases. Much of the earlier work on the antiseptic action of mercury was done on the bichloride of mercury. It is now recognized that simple mercury compounds are not germicidal in the great dilutions previously reported, and under certain conditions are not reliable disinfectants as was once claimed. They have a limited germicidal activity on nonsporulating bacteria and cannot be relied upon to kill bacterial spores even after many hours' exposure.

In recent years special efforts have been made to develop compounds which would retain the germicidal and antiseptic powers of mercury and, at the same time, be relatively nontoxic and nonirritative. Solutions of compounds of mercury with dyes or other organic radicals have been developed for the treatment of bacterial infections. In general they are highly bactericidal and are less toxic and less irritating than the chlorides, iodides, and cyanides of mercury, but it has not been conclusively demonstrated that they are effective against bacterial spores. Some have an ability to penetrate to some depth into living tissues and to act as fairly efficient chemotherapeutic agents; the extent of this action has not been definitely established.

Pharmacological Action.—The importance of mercury rests on its germicidal, antiseptic, diuretic, antisyphilitic, and cathartic actions.

Absorption and Excretion.—Mercury is slowly absorbed from the skin by way of the hair follicles and sebaceous glands. It may be absorbed when in vapor form by the lungs, and from the intestines when a soluble salt is ingested. Mercury, by whatever route introduced, is taken up by leucocytes and transported to various organs, principally the liver, intestines, and kidneys.

Mercury is slowly but largely excreted in the feces and urine, each eliminating about an equal amount. The salt is also excreted by the salivary glands, by the stomach, and by the liver and colon. A considerable amount of mercury is stored in the bones, liver, kidneys, and muscles, and is slowly excreted over a period of several months.

Local Action.—Local action is dependent on the concentration of mercury ions and on the precipitant effects on proteins. Mercury produces effects which depend upon its property of combining with proteins to form albuminates. This union destroys the life of the cells or tissues. The albuminate of mercury is soluble in an excess of protein, a property which favors deep penetration and corrosive action. Wet dressings in concentrations of 1 to 2 per cent may cause dermatitis, while solutions of mercury bichloride may cause inflammation, vesicles, and even necrosis if the skin happens to be broken.

Local irritant action is most pronounced with mercuric chloride. Intramuscular injections cause severe pain and sometimes local necrosis. On the skin concentrations of 1 to 5 per cent produce irritation, vesication, and corrosion; sensitive skin may be inflamed by the more dilute surgical solutions. The formation of double salts of mercury, such as potassium mercuric iodide, greatly decreases its local irritation. However, its systemic action is about the same as for mercuric chloride, on the basis of mercury content.

Antiseptic Action.—Mercuric chloride is a powerful antiseptic, especially in the absence of proteins or other substances which may precipitate the mercury. The growth of microorganisms is inhibited by a 1:300,000 dilution, nonspore-formers by a 1:20,000 dilution, and anthrax bacilli by 1:1,000 dilution. Anything which unites with mercury will limit its antiseptic power by limiting its penetration and by decreasing the available mercury. Mercury may be used to disinfect the hands at a concentration of 1:1,000. It rapidly corrodes metallic instruments, which limits its usefulness for sterilizing purposes.

Antisyphilitic Action and Uses.—See Chapter IX, Antisyphilitic Drugs.

Action on the Intestines.—Mercury compounds produce intestinal irritation and subsequent catharsis. See Chapter VI, Cathartics.

Diuretic Action and Uses.—Moderate doses of mercury cause marked diuresis, especially in cases in which large accumulations of fluids are present. Large doses of mercury cause severe irritation of the kidneys, with symptoms of nephritis and even anuria. Calomel acts as a diuretic in the early stages, usually before cathartic action occurs. See Chapter XVII, Diuretics.

Action on the Nervous System.—The action of mercury on the nervous system is obscure. In acute poisoning the intellect remains clear, and no symptoms of poisoning, as a rule, are manifested, while in chronic poisoning there are symptoms of paralysis, tremors, insanity, and erethism. The tremors and erethism are due to the action on the higher centers. The general weakness is due not only to peripheral muscle and nerve pathology but also to changes in the higher centers.

Action on Circulation.—Toxic doses of mercury depress the heart muscle and vascular tone. When injected subcutaneously, large amounts of mercuric chloride cause a gradual fall in blood pressure; when injected intravenously a more sudden fall occurs. Large doses of organic arsenicals (salyrgan, merbaphen) cause rise in blood pressure. The rise in blood pressure and the volume changes in the other organs indicate a direct action on the blood vessels; marked cardiac irregularities and even ventricular fibrillation may follow such doses (D. E. Jackson, 1926).

Blood.—Large doses of mercury cause a reduction in the number of red blood corpuscles, while small doses prevent their destruction. Small doses of mercury not only cause an arrest of the destruction of corpuscles due to syphilis, but actually cause an increase up to normal. Large doses produce an opposite effect.

Toxicology.—Mercury poisoning deserves careful consideration. The majority of poisoning cases due to mercury are suicidal. When taken with suicidal intent it is practically always ingested in the form of the bichloride salt. Poisoning may occur following use of mercury in the vagina for the prevention of conception. Many cases have occurred following accidental ingestion of a tablet of mercury.

INCIDENCE.—The fashion or "vogue" in suicide changes with the years. Carbolic acid was once quite popular but gave way to opium derivatives. Then, and especially from 1920 to 1930, bichloride poisoning became very frequent. From 1930 to the present mercury poisonings have been slightly less frequent, whereas poisoning due to barbiturates, potassium cyanide, and lysol have been more common.

A. Acute Poisoning.—SYMPTOMS.—The symptoms of mercury poisoning are associated with damage to (1) the circulatory system, (2) corrosive action on the digestive tract, and (3) its effects on the kidneys.

Circulatory System.—Shock may appear early after poisoning, or it may be seen late in the course of an ulcero-hemorrhagic colitis. Typical symptoms of pallor, weak and rapid pulse, low blood pressure, subnormal temperature, syncope, and collapse are present.

Gastrointestinal Tract.—The initial symptoms may be vomiting and retching which frequently occur during the first five to fifteen minutes. Usually soon after ingestion the patients complain of burning, metallic taste, thirst, soreness in pharynx, and soon abdominal pain. Marked swelling of the membranes may occur. Vomiting may be bloody, accompanied by severe purging with liquid and later bloody stools. Rectal pain and tenesmus are often present.

Kidneys.—Very mild cases may show no demonstrable kidney pathology. In more severe cases, however, oliguria followed by anuria may set in within one to three days. In cases going on to suppression, the urine shows marked albuminuria, and hematuria. With the appearance of oliguria—and certainly after anuria—the nitrogenous elements in the blood quickly rise. A fatal case may have blood urea in the hundreds of milligrams, with a corresponding high creatinine.

Uremia contributes its element of nausea and vomiting, and there may be drowsiness, hiccup, twitching of the muscles and, finally coma. There is rarely a rise in blood pressure and, despite the anemia, edema does not occur.

PROGNOSIS.—Prognosis should be guarded. However, if 5 grains or less of the drug are taken, the outcome almost certainly will be good. If the emesis interval is known to be less than thirty minutes, the prognosis is usually good. But vomiting after mercury ingestion may be incomplete and ineffectual. Hence the length of time until actual therapeutic lavage is of prime importance. A marked leucocytosis of 20,000 or more almost always proves serious. Uremia is usually a serious symptom, but occasional recoveries occur after a long suppression. If the nonprotein nitrogen continues to increase after the fourth day, the prognosis is very grave. If the nonprotein nitrogen goes down after the seventh day, the patient may recover.

TREATMENT.—*Emergency Treatment:* This is very important. Instructions over the telephone may be lifesaving even if only partially carried out. *Instructions:* Administer 1 pint of milk (skim milk is preferred as fats aid mercury absorption). If no milk is available administer 1 pint of water. Follow milk or water by ingestion of two or three whole raw eggs. Next induce vomiting with lukewarm salt water, mustard water, etc. On arrival of physician repeat above treatment up to emesis. Then give a gastric lavage.

Treat the rare phenomena of shock by the application of hot blankets and inject 0.1 cc. of coramine subcutaneously. Morphine may be indicated later. Plasma transfusions may be indicated.

Remember that the patient may still be bent on self destruction and may deny taking the poison or may attempt further harm to himself. Therefore do not leave patient unattended.

BAL.—After repeated gastric lavage and emesis, injection of BAL (2,3-dimercaptopropanol) should be given. The dose recommended is 1.2 cc. of 10 per cent solution per 100 pounds of weight, given intramuscularly four times daily for two days and diminished thereafter. Best results are to be expected if treatment is begun within three or four hours. Delayed treatment with BAL still may be of value.

Longscope, et al. (1946) at the Johns Hopkins Hospital recommended that BAL be given in an initial intramuscular injection of 300 mg. followed within the first twelve hours by two or even three injections of 150 mg. each. He found the mortality rate to be 4 per cent compared to 12.9 per cent before BAL treatment was introduced. The total experiences with BAL in mercury poisoning are so limited that categoric statements may not be made. Any further treatment should be on a symptomatic basis.

Sodium thiosulfate (1 Gm. in 10 cc. of aqueous solution) intravenously, once or twice daily, has been recommended. Its use has been based on the theory that it effects the conversion of the poison into the harmless mercury sulfide. Rosenthal (1935) recommends the use of a gastric lavage containing 5 per cent solution of *sodium formaldehyde sulfoxylate,* leaving 200 cc. in the stomach; this is followed immediately by intravenous administration of 10 grams in 100 to 200 cc. of water. This drug acts by reducing the mercuric chloride to mercurous compounds.

Colon irrigation, twice daily for a few days, and gastric lavage twice daily, may serve to remove any mercury still remaining in the lower bowel. Lambert and Patterson recommend daily sweats in hot packs, but this is contraindicated if the circulation is poor.

Further Therapy.—Hospitalization is usually indicated. Only here can proper study and treatment be administered. Immediate and intensive efforts to prevent further absorption of re-excreted mercury should be instituted. In addition, force large quanities of alkaline drinks and parenteral fluids in order to dilute toxins and promote their elimination by all possible channels. Add to these general measures, frequent routine checks of the blood for hypochloremia and acidosis.

Routine Treatment:

Fluids by Mouth.—Administer 8 ounces of the following every four hours.

℞

Potassium Bitartrate	4 Gm.
Sugar	4 Gm.
Lactose	15 Gm.
Lemon Juice	30 cc.
Water q.s. ad	500 cc.

Alternate with this drink 8 ounces of milk every four hours. Urge these drinks even in cases of vomiting.

Gastric Lavage.—Perform gently with warm water until several washings remain negative for mercury. A mild soda solution may be used.

B. Subacute Poisoning.—This condition may develop from the administration of mercury as a purgative or from its use in syphilis. It is

due to an accumulation of mercury in the body caused by slower elimination than absorption. The usual symptoms are fetid breath, bad taste, swollen gums, and salivation. Abdominal pain, purging, and bloody stools often occur. *Treat* by stopping the administration of mercury and by giving opiates and demulcents. For hygiene of the oral cavity, a mouthwash containing potassium chlorate is recommended.

To prevent or relieve excessive salivation:

℞

Potassium chlorate	10.00 Gm.	(3iiss)
Tannic acid	0.25 Gm.	(gr.iv)
Distilled water q.s. ad	300.00 cc.	(f℥x)

M. Sig.: Use as mouthwash.

C. Chronic Poisoning.—Workers exposed to mercury vapor, such as miners and mirror makers, may develop chronic mercury poisoning. The condition may follow the continued use of the drug as in the treatment of syphilis. The usual symptoms are anorexia, loss of weight, anemia, diarrhea, muscular weakness and peripheral neuritis. Stomatitis, fetid breath, and the development of a blue line near the teeth are common symptoms. Cachexia and necrosis of the jaw may be associated with the chronic type of poisoning.

The blood picture is not specific, but there is a decrease in red cells and the mononuclears are increased. Nervous symptoms, such as polyneuritis, are often present. The higher centers may be affected, characterized by nervousness and apprehension. There may be a slight twitching of the facial muscles and a fine tremor of the fingers. Delicate movements become impossible, whereas coarse work may be conducted quite normally.

THERAPY.—In *chronic* poisoning the dermatitis may soon disappear after removal of patient from the source of the poisoning. Astringents may be used for stomatitis. A satisfactory diet and hygienic regime for the patient must be established. If tremor is present, alternate galvanic and faradic stimulation may be indicated. The use of sodium thiosulfate may be of value, gr. 15 (1 Gm.) in 10 cc. of sterile water intravenously every other day for a short time.

FATAL DOSE.—Three grains of mercury by ingestion have been reported as fatal. Such instances are rare. On the other hand, huge doses have been taken with recovery, but again such cases are exceptional. Certain factors besides the actual dosage plays an important role. The same dose in solution has proved much more fatal than ingestion of tablets as such. Furthermore the ingestion of the drug on an empty stomach is more serious than when taken after a full meal. The prior ingestion of alcohol usually causes a higher fatality rate.

Any given dose of mercury may often prove fatal or nonfatal, depending entirely on the emesis interval. Usually the fatality period is directly proportional to the length of the emesis interval.

FATAL PERIOD.—Death has occurred within half an hour after ingestion of mercury, but such cases are rare. Fatalities may occur within a few hours due to shock. Of the fatal uremic cases, many patients die within five days, but occasionally they may live for weeks.

PATHOLOGY.—Ingested mercury produces local inflammatory changes wherever it contacts the mucous membrane. Lesions may extend part way down the gastrointestinal tract or the entire distance. Absorption of the drug is of greater import, as it is rapidly taken up from the stomach and intestine and passes into the circulation. From here it is re-excreted into the alimentary canal, especially to the stomach and

colon. Rather large quantities of mercury may pass through the liver into the bile and thus cause additional injury.

By far the greatest damage is to the kidneys. This damage may occur experimentally in animals five minutes after the introduction of mercury into the stomach. Thus any therapy may not be of much value. Finally, the combination of persistent vomiting and diarrhea plus nephrosis induces a definite lowering of blood chlorides as well as occasionally causing acidosis—all facts to remember in therapy.

POSTMORTEM CHANGES.—The essential postmortem changes are those of damage to the alimentary tract and to the kidneys. All degrees of gingivitis, glossitis, pharyngitis, gastritis, colitis are seen. Lesions may vary from hyperemic or hemorrhagic, to gangrenous. The kidneys present a typical nephrosis with swelling and necrosis of the tubular epithelium. The liver may show fatty and parenchymatous degeneration, and the myocardium may also show similar changes.

Therapeutic Uses.—*Administration of Mercury.*—Care should be exercised that toxic compounds are not formed. Particular consideration should be given to this when the patient is taking iodides. Before beginning the use of mercury the teeth should be examined and cared for. Frequent urine analyses should be taken throughout the course of its use.

SKIN DISEASES.—Ointment of Ammoniated Mercury, the most irritating of the official ointments, is employed in the treatment of *chronic eczema, impetigo, psoriasis,* and in *head and body louse* and *crab louse infections.* The solution of acid nitrate of mercury, which is very caustic and penetrating, is used sometimes for the destruction of *syphilitic sores, lupus, condyloma, warts,* and like conditions. Yellow Oxide of Mercury has been used with advantage in *eczema, seborrheic dermatitis, acne,* and *erythematous pruritus of the anus.* The red oxide and the oleate of mercury are of value in *parasitic skin diseases* and *ulcerative processes,* such as often accompany venereal disorders.

For psoriasis:

℞

Ammoniated Mercury	0.60-6.00 Gm. (gr.x-3iss)
Petrolatum	60.00 Gm. (℥ij)

Mix.

Sig.: Apply twice daily.

For eczema:

℞

Ammoniated Mercury	0.30-1.30 Gm. (gr.v-xx)
Zinc Oxide	
Starch ——— āā	15.00 Gm. (3iv)
Petrolatum	30.00 Gm. (℥j)

Mix.

Sig.: Apply as directed.

For crab louse infection:

℞

Ammoniated Mercury	6.00 Gm. (3iss)
Lanolin	30.00 Gm. (℥j)
Petrolatum q.s.	60.00 Gm. (℥ij)

M. Sig.: Apply as directed.

PREPARATIONS

Mercury Oleate, *Oleatum Hydrargyri*, U.S.P. Contains about 25 per cent mercuric oxide and a small amount of uncombined Oleic acid. *Caution.* Oleate of mercury must not be dispensed if globules of mercury have separated. *Uses:* In the preparation of strong mercurial ointment.

Strong Mercurial Ointment, *Unguentum Hydrargyri Forte*, U.S.P. (Mercurial Ointment). Metallic mercury (about 50 per cent) and oleate of mercury (4 per cent) with wool fat, white wax, and white petrolatum. *Uses:* to secure the systemic effect of mercury by inunction.

Mild Mercurial Ointment, *Unguentum Hydrargyri Mite*, U.S.P. Contains about 10 per cent mercury. Strong mercurial ointment 20 per cent with white ointment 80 per cent. *Uses:* Locally against pediculosis but may be irritant to the skin.

Ammoniated Mercury Ointment, *Unguentum Hydrargyri Ammoniati*, U.S.P. Ammoniated mercury (5 per cent) in white ointment.

For Antisyphilitic, Cathartic, and Diuretic Uses of Mercury, See Index.

Antiseptic Use.—The antiseptic action of the simple compounds of mercury depends upon the concentration of the mercuric ion in solution, their precipitant action on protein, and their affinity for the protein under the conditions used. The use of simple mercury compounds is limited by their toxic action on man and animals, their irritant and toxic action on tissues, their corrosive action on metals, and their tendency to precipitate proteins.

Mercury compounds commonly used for disinfectant and antiseptic purposes include mercury bichloride, ammoniated mercury, mercuric cyanide, potassium mercuric iodide, phenylmercuric compounds, merbromin (mercurochrome), merthiolate, and nitromersol (metaphen).

Mercury Bichloride

Mercury bichloride, corrosive sublimate, $HgCl_2$, is a heavy white powder, soluble in water (1:13.5), alcohol (1:3.8). It is nearly universally incompatible.

Pharmacological Action.—The action of mercury, as well as that of many other heavy metals, is a complex process, and appears to take place as follows: The metal is first adsorbed upon the surface of the bacteria, then it penetrates and kills the bacteria. The absorption takes some time. Any other substance that can absorb mercury, such as proteins, serums, etc., will prevent mercury from acting effectively on bacteria. The disinfecting action of mercury is proportional to the amount of ionized mercury present. Mercury combines with protein material to form a precipitate which is soluble in albumin and sodium chloride solutions. In order to prevent precipitation of mercury proteinate and to decrease irritation, it is customary to add an equal quantity of sodium chloride or ammonium chloride as is done in commercial bichloride tablets.

The practical usefulness of mercury bichloride is limited by the following factors: (1) interference of organic matter, hence poor penetration, (2) local and systemic toxicity, and (3) its action in low concentrations is very slow.

Therapeutic Uses.—Mercury bichloride is used as an *antiseptic* and *germicide;* also as a specific *antisyphilitic agent.* For many years a 1:1,000 solution has been used for such purposes as disinfecting mucous

membranes and wounds and for sterilizing the hands of the surgeon. Concentrations of 1:20,000 to 1:2,000 must be used with caution. A 1 per cent alcoholic solution is indicated for *conjunctival ulcers.* A 1:2,000 solution in solution of hydrogen peroxide is still recommended as a *mouthwash* in Vincent's and other infections of the mouth. Its use in the irrigation of large serous or mucous surfaces should be discouraged, as serious poisoning may result. Deaths have resulted from application to the digestive tract, vagina, and broken skin. A dilution of 1:50,000 kills some bacteria and a 1:100,000 solution is antiseptic. Most spores are killed by a 1:500 solution.

Preparations

Mercury Bichloride, *Hydrargyri Bichloridum,* N.F. Heavy, colorless crystals, crystalline masses or white powder, odorless and with a characteristic metallic taste. *Dosage:* 4 mg. (1/15 grain) in solution or pills. Hydrargyri Perchloridum, B.P., 0.002-0.004 Gm. (1/32-1/16 gr.).

Mercury Bichloride Large Poison Tablets, *Toxitabellae Hydrargyri Bichloridi Magnae,* N.F. Each tablet contains about 0.5 Gm. (8 grains) of mercury bichloride.

Mercury Bichloride Small Poison Tablets, *Toxitabellae Hydrargyri Bichloridi Parvae,* N.F. Each tablet contains about 0.125 Gm. (2 grains) of mercury bichloride.

Ammoniated Mercury

Ammoniated mercury is a white powder containing about 80 per cent of mercury in the form of $HgNH_2Cl$. It is insoluble in water or alcohol. *Ammoniated Mercury Ointment,* White Precipate Ointment, is commonly employed in medicine. The ointment consists of Ammoniated Mercury (5%) in white ointment (white petrolatum 90%, wool fat 5%, and white wax 5%).

Action and Uses.—Ammoniated mercury is an antiseptic, a parasiticide, a mild stimulant, and an antiseborrheic. It stimulates healthy inflammatory reaction in *psoriasis.* It is a favorite ingredient of freckle removers and bleach creams, alone or in combination with salicylic acid.

The 5 per cent ointment is useful in treating *boils, furuncles, ringworm,* etc. It is used in 5 per cent strength for suppurating *dermatoses;* 2 to 3 per cent for *seborrhea;* 10 per cent ointment for *crab louse* infection. In the treatment of *pinworms* 2 per cent of ammoniated mercury in equal parts of lanolin and petrolatum may be applied to the anal region and perineum. Ammoniated mercury is an excellent antipruritic remedy in pruritus ani.

℞

Ammoniated Mercury	2.4 Gm.	(gr.xl)
Lanolin	60.0 Gm.	(℥ij)
Petrolatum q.s. ad	120.0 Gm.	(℥iv)

Mix and make an ointment.

Sig.: Apply to itching area.

Ammoniated Mercury Ointment may be used in the official strength on coccigenic *impetigo* or *psoriasis.* It is the ointment of choice in the treatment of psoriasis of the scalp. Salicylic acid in strengths of 2 to 5 per cent may be added to facilitate the removal of scales. In full strength Ammoniated Mercury Ointment is an excellent prepara-

tion to use on a dressing for *furuncles* and *sycosis* of the neck. It may be diluted with four parts of Baro (borated cold cream—boric acid 5 parts, ointment of rose water 95%) for use on very young infants.

PREPARATIONS

Ammoniated Mercury, *Hydrargyrum Ammoniatum*, U.S.P., B.P. (White Precipitate).

Ammoniated Mercury Ointment, *Unguentum Hydrargyri Ammoniati*, U.S.P. Ammoniated Mercury (5%) in white ointment, B.P., 5 per cent ammoniated mercury.

Mercuric Cyanide

Mercuric cyanide, $Hg(CN)_2$ (N.F.), the mercuric salt of hydrocyanic acid has been reported to be less irritating than mercuric chloride and equally as antiseptic. It is used in a similar manner to mercuric chloride.

Locally, solutions of from 1:4,000 to 1:2,000 may be used for applications to the eye or mucous membranes; from 25 to 35 minims of a 1 per cent solution may be used hypodermically without untoward reactions. A 0.01 per cent solution has been used as a gargle in diphtheria and croup.

Potassium Mercuric Iodide

This complex salt, K_2HgI_4, is formed by the interaction of one molecule of mercuric iodide with two molecules of potassium iodide. It is indicated for the same purposes as mercuric iodide, but has the advantage of being more soluble. It is about one-half as toxic as mercuric chloride on the weight basis.

Externally, potassium mercuric iodide is used for skin infection, irrigations, and for disinfection of instruments. It is used as a disinfectant in concentrations of 1:100 to 1:10,000. For wound irrigation make up solutions using 0.9 per cent sodium chloride.

Solutions are made by dissolving the salt in water containing an excess of potassium iodide equivalent to about 20 per cent by weight of the amount of potassium mercuric iodide used. The potassium iodide tends to prevent decomposition and precipitation of mercuric iodide. Another method of preparing potassium mercuric iodide is to dissolve 1 part by weight of mercuric iodide and 1 part by weight of potassium iodide in water and dilute as desired; such a solution contains the proper excess of potassium iodide.

Phenylmercuric Compounds

Phenylmercuric compounds possess effective bacteriostatic and bactericidal activity against certain pathogenic microorganisms. The activity of these compounds is primarily attributable to the phenylmercuric ion. In general, phenylmercuric salts are highly ionized in solution to provide phenylmercuric ions $(C_6H_5Hg)^+$. Chlorides, bromides, and soaps precipitate the phenylmercuric salt in solutions of acid, neutral or slightly alkaline reaction. The chloride and bromide are quite insoluble; for this reason the more soluble basic phenylmercuric nitrate and other salts are preferred.

Aqueous solutions containing phenylmercuric ions buffered with inorganic or organic acids, are fairly stable. Buffering also makes the preparation less irritating to tissues, noncorrosive to metals and rubber. The stability is relatively good in organic solvents. Solutions of phenyl-

mercuric salts, however, slowly develop increasing amounts of mercuric and mercurous ions or free mercury, as the result of gradual decomposition of phenylmercuric ions.

These compounds possess a comparatively high germicidal and inhibitory action against a variety of pathogenic microorganisms and are relatively nontoxic to human tissue. They may, however, produce irritation or poisoning in occasional individuals with undue sensitivity. The toxicity is directly proportional to the concentration of phenylmercuric ions.

Like other organic mercurial antiseptics the phenylmercuric compounds do not kill bacterial spores even after several hours' exposure. The presence of buffered solutions of phenylmercuric salts does not interfere with the precipitin reaction of human serum, the action of compliment, the action of pepsin or trypsin, or the antigenic power of vaccine; serum proteins are not precipitated and blood is not hemolyzed.

MERPHENYL NITRATE (Basic), $C_6H_5HgNO_3C_6H_5HgOH$, is recognized for external use as an ointment or in solution for disinfection of the skin, abrasions, lacerations, wounds, and infections.

Aqueous buffered solutions (1:1,500) may be used for prophylactic disinfection of the skin and minor lesions: Dilute *above* ten to fifteen times for application to mucous membranes. A 1:24,000 dilution plus 0.5 per cent sodium chloride is indicated for use as a wet dressing. For minor injuries a 1:1,500 oxycholesterin base ointment is recommended.

PHENYLMERCURIC PICRATE, $C_6H_5HgOC_6H_2(NO_2)_3$, in the form of a tincture may be used as a prophylactic disinfectant in the preoperative preparation of the intact skin and for recent abrasions, lacerations, and wounds. The tincture consists of phenylmercuric picrate 0.5 per cent, picric acid 1.2 per cent, acetone 10 per cent, alcohol 50 per cent, water 38.3 per cent. For prophylactic preoperative skin preparations, disinfection of tissue injuries, and superficial infections use full strength tincture; for wet dressings and continual irrigation dilute the 1:200 tincture approximately seventy-five times. To prevent tincture concentration add about 0.5 per cent sodium chloride to diluted solution.

MERPHENYL BORATE, $C_6H_5HgBO_3.H_2O$, is recognized for use in the tincture form as an antiseptic for disinfection of the skin, superficial injuries, and wounds. The tincture consists of phenylmercuric borate 0.2 per cent, boric acid 1 per cent, acetone 4.6 per cent, alcohol 43.2 per cent, water 50 per cent, sodium acid phosphate 1 per cent. The tincture may be applied full strength to skin and superficial wounds. On mucous membranes dilute the tincture about forty-five times with water. When used for wet dressing add to diluted solution 0.5 per cent sodium chloride.

Merbromin (Mercurochrome)

Merbromin, N.F., Mercurochrome (220-Soluble), is the disodium salt of dibromohydroxymercurifluorescein. It is stable, freely soluble in water and soluble in alcohol and contains 24 to 26 per cent mercury. Being an organic compound of mercury with the dye molecule (fluorescein), it is less irritating than ordinary mercury salts and does not precipitate proteins.

Pharmacological Action.—Merbromin is a nonirritating moderately active antiseptic which penetrates significantly only into dying or dead tissue. A 2 per cent aqueous solution of Merbromin acts more slowly than Iodine Tincture, U.S.P., but has more prolonged bacteriostatic effect. The drug is well tolerated in a strength of 1 per cent by the bladder and urethra, and a 2 per cent solution may be

used in the anterior urethra. No systemic effects have been observed following its local application in human beings. The aqueous-alcohol-acetone solution called Surgical Merbromin Solution is more active than the aqueous solution and is indicated for preoperative skin disinfection.

Therapeutic Uses.—In 1 to 5 per cent solutions, it may be used as an antiseptic on mucous membranes and the skin. A 2 per cent solution is advertised as a *first aid antiseptic;* as such, it is apparently just below tincture of iodine as a surface antiseptic. A 2 per cent solution is a safe collyrium for infection of the *conjunctiva* or for *corneal ulcer.* A 1 to 2 per cent solution has been recommended as a *genitourinary antiseptic.* The intravenous use may be followed by severe toxic symptoms. Solutions are self-sterilizing and should not be boiled. Stains may be removed by application of sodium hypochlorite solution.

Merbromin Solution, N.F., a 2 per cent solution in water; *Surgical Merbromin Solution,* N.F., a 2 per cent solution in water (35%), acetone (10%) and alcohol are available.

Merthiolate

Merthiolate, sodium ethylmercurithiosalicylate, N.N.R., is crystalline, stable in air, soluble in water (1:1) and in alcohol (1:8). It contains 49.15 to 49.65 per cent mercury in organic combination.

Merthiolate is an effective germicide of low toxicity which is free from any tendency to coagulate proteins. It is useful for disinfecting tissue surfaces.

It is useful for disinfection of instruments in 1:1,000 aqueous solution; for skin disinfection, tincture 1:1,000; for application to wounds, aqueous solutions 1:1,000; for ophthalmological use, aqueous solution, from 1:10,000 to 1:5,000; for urethral irrigations, 1:30,000 to 1:5,000 aqueous solutions.

Nitromersol (Metaphen)

Nitromersol, N.F., Metaphen, the anhydride of 4-nitro-3-hydroxy-mercurioorthocresol, contains 57 per cent mercury in organic combination. It is a yellow powder, insoluble in water, very slightly soluble in acetone, and soluble in alcohol. It is used only in the form of the sodium salt. Various preparations such as ointments, tinctures, and solutions are available.

Action and Uses.—Nitromersol is a germicide said to be stronger than mercuric chloride, Merbromin, and other organic mercury compounds, and 500 times stronger than phenol. It is relatively nonirritating to skin and mucous membranes, nontoxic, and precipitates albumin slightly. Alcoholic solutions do not corrode metallic instruments.

Solutions of Nitromersol in water are prepared with the aid of sodium hydroxide. For *disinfection of instruments* solutions of 1:5,000 to 1:1,000 are recommended; for *skin disinfection* solutions of 1:5,000 to 1:1,000; for *eye* and *urethral irrigation* solutions of 1:5,000 to 1:10,000 are suggested.

SILVER COMPOUNDS

Silver preparations are used in medicine to secure caustic, astringent, and antiseptic effects. There are various classes of silver preparations, the most important of which are: *Simple silver salts* (silver nitrate) and *colloidal silver preparations* (colloid silver iodide compound, silver

protein compounds). The antiseptic action and the irritant properties of silver preparations are due chiefly to two factors, namely, the presence of free silver ions and the mode of administration.

Silver Nitrate

Silver nitrate is a colorless, odorless, crystalline salt soluble in water (1:0.4) and in alcohol (1:25). It is incompatible with haloids, hydroxides, carbonates, organic drugs, and reducing agents.

Pharmacological Action.—When caustic effects are desired, silver nitrate is the silver compound of choice, because the colloidal silver compounds are comparatively free of caustic properties.

As an *astringent*, also, silver nitrate is the compound of choice, but it must be used in weaker solutions. The *antiseptic* action of silver nitrate is complicated by irritation, pain, astringency, and corrosion. Simple silver salts are usually indicated in the treatment of indolent wounds and for the destruction of tissue.

Mode of Action.—The antiseptic powers of simple silver salts, such as silver nitrate, are due to silver ions and may be divided into three phases:

1. Immediate germicide and irritant action.
2. The "oligodynamic" action of finely divided silver resulting from the reduction of the silver ions. The oligodynamic action of metals is defined as the catalytic formation of hydrogen peroxide due to the presence of small amounts of metallic ions.
3. The antiseptic action produced by the re-solution of the silver protein compounds formed.

Toxicology.—Long-continued use of any of the silver compounds results in *argyria*, a condition which is due to the deposition of silver particles in the skin. The *symptoms* of poisoning are pain in the throat and stomach, vomiting and purging of a black material, coma, and respiratory collapse. The lips, which at first may be a gray white, later become black.

The *fatal dose* varies from 2 to 15 grams. *Post-mortem findings* are those of local caustic action and stains on the mucous membranes of the esophagus and gastrointestinal tract. The gastric contents and the parenchymatous organs are used for toxicological examination. *Treatment:* Lavage of the stomach with dilute sodium chloride; follow with demulcents.

Therapeutic Uses.—Silver nitrate is used little internally; however, it has been recommended to reduce the gastric secretion in *hyperchlorhydria.* In solutions of 2 to 5 per cent, it may be used to cauterize indolent *ulcers, chancres,* and *mucous patches,* followed by a solution of sodium chloride to remove the excess silver. For *general antiseptic* and *astringent* action an aqueous solution varying from 1:10,000 to 1:1,000 is recommended. A drop of fresh 1 per cent solution instilled into the eyes of newly born infants is effective as a prophylactic against *gonorrheal ophthalmia neonatorum.* After three minutes the eyes are irrigated with physiological saline. Solutions of 2 to 10 per cent are recommended for *pharyngeal* and *laryngeal conditions;* solutions of 1:10,000 to 1:2,000 are used for *bladder irrigation.* Argyria may follow prolonged use of all silver compounds.

Silver Picrate

Silver picrate, $C_6H_2(OAg)(NO_2)_3 + H_2O$ (N.N.R.), is an ionizable silver salt which combines the antiseptic properties of both the silver and

picrate ions. It is a yellow crystalline compound sparingly soluble in aqueous and organic solvents.

Silver picrate is useful in the treatment of urethritis and infection of Bartholin's and Skene's glands by *Trichonomas vaginalis*, and *Monilia albicans vaginitis*. It is recommended that 5 Gm. of a compound powder (1 part silver picrate : 99 parts kaolin) be applied to the vaginal wall by insufflation. Supplementary treatment with silver picrate suppositories has been recommended. There is danger from argyria or renal damage if silver picrate is used over long periods of time. It is therefore necessary to watch the skin for signs of argyria, and the urine for albumin and casts.

Colloidal Silver Preparations

In the silver preparations of this class, the silver does not exist to any great extent as free ions; therefore it does not precipitate chlorides or proteins, and is nonirritant and noncorrosive. The antiseptic action is due to the liberation of a very low concentration of silver ions, which vary for the different compounds.

Mode of Action.—The mechanism of action is analogous to the *late action* of silver nitrate by re-solution of the protein silver compounds.

The colloidal silver compounds may have advantages over silver nitrate solutions by being nonirritant, and by their lack of protein precipitation which facilitates access of antiseptic to the cells. These solutions form more concentrated solutions than are likely to be formed from the re-solution of the silver precipitates. Furthermore, the colloidal particles may be smaller and therefore more reactive.

Pharmacological Action.—Colloidal silver preparations are indicated primarily for antiseptic use on mucous membranes. Strong protein silver is most effective but it is slightly irritant and stimulant. Mild protein silver acts largely as a demulcent, protective, and detergent. Collargol acts locally like mild protein silver, but is indicated to produce systemic reactions.

Therapeutic Uses.—For application to mucous membranes concentrations of from 0.1 to 10 per cent strong protein silver are recommended; from 5 to 50 per cent of mild protein silver, and from 0.02 to 1 per cent collargol. Solutions should be recently prepared and be protected from light. They may be applied every two to five hours if necessary. Ointments and suppositories are used in the same concentrations as aqueous solutions.

Representative colloidal silver compounds fall into the following groups: (1) Strong Type Protein Silver; (2) Mild Type Protein Silver; (3) Collargol Type, (4) Electric Type (dilute and quite unstable), and (5) Silver Halides.

Strong Protein Silver

Strong Protein Silver, a silver and protein compound containing about 8 per cent silver, is soluble in water (1:2) and insoluble in alcohol. It is mildly irritant and is not precipitated by chlorides.

Action and Uses.—Although it contains less silver than the mild protein silver, its therapeutic action lies between that of silver nitrate and mild silver protein. It is efficacious in the prophylactic treatment against gonorrheal infection.

It is employed in mucous membranes in concentrations of 1 to 10 to 1 to 1,000. The same concentrations are employed for making up ointments or suppositories. Stains on linen may be removed by mercuric chloride 1:1,000.

Mild Silver Protein

Mild Silver Protein contains about 20 per cent silver. It is hygroscopic and freely soluble in water, and insoluble in alcohol. The solution should be made up fresh in distilled water and protected from light. The activity of the solution is doubled in one to two weeks, and it becomes more irritant.

Action and Uses.—The preparation is nonirritant, except in stronger solutions, and is not precipitated by chlorides. The preparation is usually used in from 10 to 40 per cent aqueous solutions.

Solutions from 1 in 2 to 1 in 20 are used on mucous membranes. The same concentrations may be employed in ointments or suppositories.

Collargol

This preparation contains a much higher percentage of silver (78%), said to be in the form of metallic silver, reduced to the colloidal form by chemical means and stabilized by a small amount of egg albumin (22%). Collargol differs from mild protein silver in degree rather than in principle; it contains a larger proportion of silver in the form of colloidal metal and oxide and a smaller proportion in the form of silver proteinate. This preparation is used mainly for intravenous and intramuscular injection. The therapeutic response may be due to foreign proteins, rather than to the silver.

Silver Halides

Silver halides are mixtures of the colloidal silver salts. Colloidal Silver Iodide and Colloidal Silver Chloride are typical examples.

Colloidal Silver Iodide contains about 20 per cent silver iodide, rendered colloidally stable with gelatin. This substance is freely soluble in water. Solutions should be freshly prepared and dispensed in amber-colored bottles.

The gelatinized preparation containing 20 per cent silver iodide is used in solution or ointment as a nonirritant antiseptic for topical application against skin and mucous membrane infections. Solutions of 5 to 50 per cent are used on the skin, eye, ear, and mucous membranes of the nose, throat, and genitourinary tract. Solutions over 25 per cent may be made by dissolving in hot water. Solutions tends to precipitate after standing longer than one week. Five per cent ointments are applied externally or in the form of suppositories in the vagina.

Colloidal Silver Chloride contains about 10 per cent silver chloride rendered colloidal by a suitable stabilizing agent such as sucrose. It is an odorless, hygroscopic powder affected by light. It is freely dispersible in water.

In ophthalmia neonatorum, and other inflammatory conditions of the eye, ear, nose, throat, and skin, dilute a 100 per cent "solution" 9 to 3 parts of water. In urethral injections use dilutions of 19 to 3 parts of water.

Preparations

Silver Nitrate, *Argenti Nitras*, U.S.P., B.P.

Strong Protein Silver, *Argentum Proteinicum Forte*, N.F. Contains about 8 per cent of silver. The analogous B.P. compound is Argentoproteinum, Silver Protein. It consists of 7.5 to 8.5 per cent silver.

Mild Silver Protein, Argentum Proteinicum Mite, U.S.P. Contains about 20 per cent silver.

Colloidal Silver Iodide, *Argenti Iodium Colloidale*, N.F.

Colloidal Silver Chloride, *Argenti Chloridum Colloidale*, N.F.
Silver Picrate, *Silver Trinitrophenolate Monohydrate*, N.N.R.
Neo-Silvol, and *Lunosol*, see N.N.R.

OXIDIZING AGENTS

Many agents containing an excess of oxygen in their molecule are available as antiseptics. Oxygen is only antiseptic when in its nascent state, and in this state it is capable of almost immediately oxidizing all organic materials. Nascent oxygen may be obtained from such substances as ozone (O_3), hydrogen peroxide (H_2O_2), potassium permanganate ($KMnO_4$), sodium perborate ($NaBO_3.4H_2O$), and the metallic peroxides.

Organisms vary tremendously in their resistance to oxidizing agents although, as a rule, the gram-positive organisms are more susceptible to changes in oxidation-reduction potential of their environment. Molecular oxygen apparently is only destructive to those anaerobic organisms which produce hydrogen peroxide and do not produce catalase with which to destroy it.

Chlorine, also a widely used oxidizing agent, oxidizes by other mechanisms than releasing oxygen. (See chlorine compounds.)

Hydrogen Peroxide

Absolute hydrogen peroxide is an oily, colorless liquid. Owing to its tendency to explode and because of its caustic properties it is not used in medicine. Pharmacopoeial Hydrogen Peroxide Solution contains 2.5 to 3.5 per cent hydrogen peroxide; it is slightly acid in reaction, and deteriorates with age. It yields ten volumes of oxygen.

Action and Uses.—The solution yields oxygen when it comes in contact with pus and the nascent oxygen has a nonirritating, mild disinfectant action. Since the solutions of hydrogen peroxide have a high surface tension, they do not penetrate well and in the presence of excessive amounts of organic matter their germicidal action is feeble and not prolonged. The evolution of gas has a mechanical cleansing effect, for it loosens pus and other organic matter.

In dilution of 1:4 in water it is an antiseptic for "anaerobes" (gingivitis, trench mouth, Vincent's infection). The same dilution is recommended as a mouthwash and for wound irrigation. Hydrogen peroxide is especially effective against trypanosomes; this organism contains catalase and it is surmized that the catalase present may be sufficient to decompose small amounts of hydrogen peroxide. Clinically, hydrogen peroxide solutions have proved effective in the treatment of *Trichomonas vaginalis* infections.

Potassium Permanganate

Potassium permanganate ($KMnO_4$) occurs as long purple crystals, soluble in water (1:14). It is unstable in contact with organic compounds and is therefore incompatible with such compounds as alcohol, glycerin, organic acids, tannin, and other substances readily oxidized.

Pharmacological Action.—Potassium permanganate is a deodorant, germicide, irritant, and astringent. It is an effective oxidizing agent, but its action is only superficial and its efficiency is limited by an excess of organic matter. It can oxidize and destroy organic poisons and is used as an oxidizing antidote for organic poisons before they leave the stomach, such as aconite, morphine, strychnine, picrotoxin and cyanide, if alkaline. It is useless against atropine, cocaine, phosphorus, and most hypnotics.

Toxicology.—The drug is an irritant to the gut and large doses may produce fatal gastroenteritis. Following administration as an antidote the stomach should be evacuated. The drug has been popularly reputed to be an emmenagogue and is a common constituent of abortifacient pills. *Treatment* of acute poisoning consists of gastric lavage, emesis, administration of albumen (raw eggs), demulcent drinks, and morphine sulfate for pain.

Therapeutic Uses.—An aqueous solution (1 to 5 per cent) is used as an *antiseptic* for sterilizing surgeons' hands. As an *antidote*, 0.05 to 0.25 gram well diluted (1:1,000) is indicated. Local application of potassium permanganate crystals, after free incision, is the recognized treatment for *snake bite*.

For the *irrigation of cavities*, 0.1 to 1 per cent concentrations may be used. Solutions (1:1,000) are widely used for injections in the treatment of *gonorrhea*, *urethritis*, and *cystitis*. Pelouze uses a daily irrigation of 1:8,000, giving an injection of 5 per cent argyrol (6 cc.) after each irrigation. Solutions of 1:500 concentration may be applied externally for excessive *sweating* of the feet. For these purposes a 1:20 stock solution stored in a glass-stoppered bottle and diluted as needed is recommended. *Dermatitis venenata* (poison ivy, etc.), especially the subacute irritation, is frequently handled satisfactorily with saturated solution of potassium permanganate.

Sodium Perborate

Sodium perborate is a white, odorless, granular salt, with a saline taste and alkaline reaction. It is soluble in water (1:40), decomposing into hydrogen peroxide and sodium metaborate, $NaBO_3 + H_2O = H_2O_2 + NaBO_2$. It combines the properties of an oxidizing antiseptic and alkalinity.

Action and Uses.—It acts as an efficient oxidizer, deodorant, and antiseptic. It is ideal for certain oral lesions, such as *pyorrhea* gum infection, but should not be used too long as a dentifrice, since its alkalinity increases as it loses oxygen. On mucous membranes, it may be used by the patient, in 2 to 10 per cent solution as a wash, or full strength for local application in *Vincent's infection*. The late Dr. Bloodgood of Johns Hopkins Hospital stated that this drug will rapidly cure more than 95 per cent of the cases, if properly applied. He recommended that a thick paste of the pure salt be spread over all the teeth, be held in the mouth five minutes, then the mouth rinsed with warm water. When the entire oral cavity is involved, a perborate gargle is indicated. It is a popular ingredient of tooth powder, and is lauded as being especially effective against Vincent's infection.

For Vincent's infection:

℞

Sodium Perborate	60.00 Gm.	(℥ij)
Sodium Bicarbonate	30.00 Gm.	(℥j)
Methyl Salicylate	4.00 cc.	(f℥j)

Mix. Make a powder.

Sig.: Teaspoonful in a glass of warm water as mouthwash every hour.

Metallic Peroxides

The metallic peroxides are compounds in which the hydrogen of hydrogen peroxide has been replaced by metals, which are readily decomposed with liberation of hydrogen peroxide or oxygen. The metallic

peroxides free this oxygen more gradually than does hydrogen peroxide. The metallic peroxides differ among themselves according to their solubility and alkalinity produced by interaction of the peroxide and water. It is also affected by the nature of the metal which goes in solution when the oxide is decomposed. The peroxides are recommended as useful agents for sterilizing water.

SODIUM PEROXIDE.—Sodium peroxide, Na_2O_2, is the sodium compound analogous to hydrogen peroxide; it contains at least 90 per cent of sodium peroxide. It is not used internally, but has been used in acne, applied in the form of a paste prepared with liquid paraffin, or as a soap to remove comedones.

Zinc Peroxide (medicinal) is a mixture of zinc peroxide, zinc oxide, and zinc hydroxide equivalent to not less than 45 per cent zinc peroxide.

Although used for the same purposes as hydrogen peroxide, it has the advantage of a slower evolution of oxygen. It may be used as a sterilized powder to make up a 40 per cent aqueous creamy suspension for application to wounds especially infected by anerobic organisms. The creamy suspension may be applied to wounds and then covered with dressings soaked in the same suspension. These dressings must be changed every twenty-four hours.

PREPARATIONS

Hydrogen Peroxide Solution, *Liquor Hydrogenii Peroxidi*, U.S.P., B.P.

Potassium Permanganate, *Potassii Permanganas*, U.S.P., B.P., CAUTION: Great care should be observed in handling Potassium Permanganate, as dangerous explosions are liable to occur when it is brought into contact with organic or other readily oxidizable substance either in solution or in the dry condition.

Sodium Perborate, *Sodii Perboras*, U.S.P. Not less than 9 per cent of available oxygen.

Medicinal Zinc Peroxide, *Zinci Peroxidum Medicinale*, U.S.P.

ACIDS

Several of the acids are used for their germicidal and antiseptic action. Some owe their action to their effect on pH and also to a specific toxic action of the undissociated molecule, e.g., boric, benzoic, and salicylic. They may also be of value in restoring the normal acidity to infected areas, thereby aiding the healing processes.

The strong inorganic acids are occasionally used as cauterizing agents (chromic acid) and for local sterilization of dangerously infected wounds. Nitric acid may be used for this purpose since it forms a firm crust and does not penetrate too deeply.

Boric Acid and Borax

Boric acid, boracic acid, $B(OH)_3$, is a weak nonirritating acid having a mild antiseptic and astringent action. It is soluble in water (1:18), alcohol (1:18), and in glycerin (1:4). Borax, sodium borate, $Na_2B_4O_7 \cdot 10H_2O$, is a transparent crystalline substance, soluble in water, alcohol, and glycerin and possesses a sweetish taste.

Pharmacological Action.—Boric acid is nonirritant and has a feeble bacteriostatic action. It increases the acidity of urine. Borax acts as a weak alkali. It dissolves mucus, lessens urinary acidity, and is used for cleansing. A concentration of about 0.3 per cent added to foodstuffs checks putrefaction, and in the past this substance was used extensively as a food preservative. Prolonged investigations

(Wiley, 1904, and others) upon the action of boric acid as a food preservative have resulted in unfavorable reports concerning its use and it is now prohibited for this purpose. Benzoic acid is used extensively at present for preserving food.

Toxicology.—Boric acid is rapidly *absorbed* from the gastrointestinal tract and to a slight extent from the skin. *Poisoning* may result if boric acid is swallowed. The usual symptoms of poisoning are cold, clammy skin, weak pulse, abdominal pain, vomiting, diarrhea, and collapse. *Treat* by gastric lavage and external heat. Caffeine, or hot coffee, may be administered as a stimulant. Administer an abundance of alkalies (fruit juices, sodium bicarbonate) and water.

Therapeutic Uses.—Boric acid may be used locally as an antiseptic and astringent dusting powder, or as the official ointment for skin irritations; or in a saturated solution (4%) as an eyewash or gargle. To render the dusting powder anesthetic and more antiseptic, add chlorbutanol (25%) or ethylaminobenzoate (5%). For example a mixture of boric acid 1, purified talc 2, chlorbutanol 1, may be used. A boric acid paste is a good *antipruritic* in dermatitis venenata.

The *glycerite of boroglycerin* is used in making washes and, in the form of boroglyceride tampons for vaginitis. The official ointment, which is used chiefly as a protective dressing on wounds and abrasions, is mildly antiseptic. It serves chiefly as an emollient dressing possessing a slightly astringent action and retains heat and moisture. The ointment is used in the conjunctival sac for mild irritation or drying.

Sodium Borate-Glycerin Tampons are recommended for the treatment of thrush vaginitis. Tampons saturated in a solution of sodium borate (1 teaspoonful) in glycerin (1 oz.) are inserted in the upper part of the vagina. The treatment is continued for three or four days.

PREPARATIONS

Boric Acid, *Acidum Boricum*, U.S.P., B.P.

Glycerite Boroglycerin, *Glyceritum Boroglycerini*, U.S.P. Boric acid and glycerin representing 31 per cent boric acid. Glycerinum Acidi Borici, B.P.

Antiseptic Solution, *Liquor Antisepticus*, N.F. Boric acid (2.5%), thymol, chlorthymol, eucalyptol, methyl salicylate, thyme oil, and menthol in alcohol and distilled water.

Boric Acid Ointment, *Unguentum Acidi Borici*, U.S.P., B.P. Boric acid (10%) in wool fat and white ointment.

Compound Sodium Borate Solution, *Liquor Sodii Boratis Compositus*, N.F. (Dobell's Solution). Sodium borate and sodium bicarbonate (each 1.5%) and liquefied phenol (0.3%) in glycerin and water.

Salicylic Acid

Salicylic acid is a white crystalline substance, slightly soluble in water (1:460), freely soluble in alcohol (1:2.7). Incompatible with solution of iron, alkalies, and alkaloids.

Action and Uses.—It is mildly antiseptic and astringent, but its best value locally is as a *keratolytic* and as a *local anesthetic* (antipruritic). Intensive use corrodes the skin and mucous membranes. For general actions of salicylates, see Chapter XI.

It is used as an *antipruritic* in 1 to 2 per cent alcoholic solutions or as an ointment (3-6 per cent). Concentrations of 2 to 5 per cent solutions, powder, or ointments are used for *parasiticide* and *keratolytic* purposes. Its caustic and keratolytic actions are made use of in compounding

preparations for the local treatment of corns. A common prescription for use in the treatment of corns is:

℞

Salicylic Acid ---------- 6.0 Gm. (3iss)
Collodion ---------- q.s. ad 30.0 cc. (f℥j)
M. Sig.: Apply locally.

Salicylic acid is a constituent of Whitfield's ointment 1 or 2 (double strength) useful in the treatment of *epidermophytosis* (ringworm).

Whitfield's Ointment (1):

℞

Salicylic Acid ---------- 3 per cent
Benzoic Acid ---------- 6 per cent
Petrolatum ---------- q.s.
Mix and stir well and make an ointment.
Sig.: Apply externally to lesions.

Whitfield's Ointment is a very satisfactory preparation to use in *seborrheic dermatitis* and in *chronic intertriginous dermatophytosis* of the toes and in *dermatophytosis* of the sole of the foot. Benzoic acid prevents the decomposition of the fats in the exfoliated material and does away with the fetid odor.

Modified Lasser's paste is an excellent antipruritic. The prescription is as follows:

℞

Phenol (Liq.) ---------- 0.3 cc. (ℿv)
Salicylic acid ---------- 0.3-0.6 Gm. (gr. v-gr. x)
Zinc oxide
Corn starch ----------āā 4-8 Gm. (3j-3ij)
Petrolatum -------q.s. ad. 30 Gm. (℥j)
M. Sig.: Apply locally as directed.

Preparations

Salicylic Acid, *Acidum Salicylicum*, U.S.P., B.P.
Salicylic Collodion, *Collodium Salicylicum*, N.F. Salicylic acid (10%) and flexible collodion.

Benzoic Acid and Sodium Benzoate

Benzoic acid has been widely used as a food preservative in concentrations of 0.1 per cent. Being relatively nontoxic and tasteless, it lends itself to food preservation. In the body, benzoic acid combines with glycine to form hippuric acid, which is excreted in the urine. Four to six grams daily may cause some gastric irritation but causes no other symptoms of any account. Large doses have systemic effects similar to salicylic acid.

Sodium benzoate has the action of benzoic acid but is less irritating. It is a mild antiseptic and is practically nontoxic.

Preparations

Benzoic Acid, *Acidum Benzoicum*, U.S.P., $C_6H_5.COOH$. Soluble in water (1 in 275) and in alcohol (1 in 3). *Dosage:* 1 Gm. (15 grains) best given in the form of soluble benzoates.
Sodium Benzoate, *Sodii Benzoas*, U.S.P., $Na(C_6H_5COO)$. *Dosage:* 1 Gm. (15 grains).

VOLATILE OILS

The volatile oils have been used since antiquity as preservatives and antiseptics, although their real value as antiseptics has not been carefully investigated. With possibly the exception of thymol, the usefulness of the volatile oils is limited by their low solubility in aqueous solution and by the fact that saturated aqueous solutions are only mildly disinfectant.

Thymol

Thymol, $C_{10}H_{14}O$, is a phenol of the benzene series, obtained from *oil of thyme* and other volatile oils. It occurs in the form of large colorless crystals, slightly soluble in water (1:1,000), soluble in alcohol, and in fixed oils.

Pharmacological Action.—Thymol is about twenty-five times as disinfectant as phenol; it possesses germicidal and fungicidal action superior to that of other volatile oils. Its toxic action is about one-half that of phenol. Thymol is also analgesic, stimulant, very slightly irritant, and possesses favorable healing properties on animal tissue.

Therapeutic Uses.—Thymol is used in combination with other agents for *mouthwashes, nasal sprays, gargles,* etc., in the treatment of such conditions as *pharyngitis, stomatitis,* and *nasal catarrh.* It has been employed against hookworms but more efficient agents are now available. Thymol is administered as a constituent of antiseptic solutions and ointments. When used against *hookworms* 5 to 7 grains of the powder should be prescribed in capsules.

Thymol is a satisfactory ingredient of mouthwashes:

℞

Thymol (sat. sol.)	60.00 cc.	(f℥ij)
Hydrogen Peroxide	60.00 cc.	(f℥ij)
Glycerin	60.00 cc.	(f℥ij)
Water q.s. ad	240.00 cc.	(f℥viij)

M. Sig.: Dilute and use as mouthwash.

Thymol has been reported useful in the treatment of *actinomycosis* and *coccidioidomycosis.*

Thymol in combination with other volatile oils may be used as an oil spray to combat excessive *nasal secretion* and for relieving the feeling of *fullness of the head.*

As oil spray:

℞

Thymol	0.03 Gm.	(gr.ss)
Menthol	0.24 Gm.	(gr.iv)
Eucalyptol	0.60 Gm.	(♏x)
Liquid Petrolatum q.s. ad	60.00 cc.	(f℥ij)

M. Sig.: Use in atomizer as nasal spray.

THYMOL IODIDE is an antiseptic used chiefly as a dusting powder. It is a light brown, mildly antiseptic and astringent mixture of thymol iodides, insoluble in both water and alcohol, but soluble in ether and oils.

A dusting powder of thymol iodide may be used in the treatment of *herpes zoster.* Apply powder and hold in place by a layer of cotton and adhesive tape.

PREPARATIONS

Thymol, *Thymol,* U.S.P., B.P. *Dosage:* Anthelmintic, divided into three doses, 2 Gm. (30 grains).

Thymol Iodide, *Thymolis Iodidum,* N.F. Contains not less than 43 per cent iodine.

DYES

Dyes are employed in medicine as antiseptics, agents against protozoa and for wound healing. They are also useful as diagnostic agents, especially for the determination of renal and hepatic functions.

Mode of Action.—The dyes have a marked specificity of action which apparently is related to the staining properties of bacteria, which in turn is dependent upon the physicochemical characteristics of the constituents of the bacterial cells. Dyes that have a special affinity for the Gram-positive organism may be designated as electropositive. They are more active in a basic medium and are called *basic dyes.* The dyes active against Gram-negative organisms, that act best in an acid medium, are called *acid dyes.*

Toxicology.—All antiseptic dyes are toxic to tissue cells as well as to bacteria. Many of the dyes, however, have a greater toxicity for microorganisms than the host cells and therefore make excellent therapeutic agents.

Antiseptic dyes may be classified quite simply on the basis of their chemical constitution. The following classification (N.N.R.) is useful: (1) Azo Dyes; (2) Acridine Dyes; (3) Triphenylmethane or Rosaniline Dyes; (4) Fluorescein Dyes; (5) Phenolphthalein Dyes; (6) Miscellaneous Dyes.

Azo Dyes

The azo dyes have a marked power of stimulating the proliferation of epithelial cells and are used in the treatment of burns, wounds, chronic ulcers, and bed sores. They are usually employed in the form of ointments or oily solutions ranging in concentration of from 4 to 8 per cent. The 8 per cent ointment may be irritating and should be alternated with a soothing ointment. They may also be employed (mixed with talc) as dusting powders.

PREPARATIONS

Scarlet Red, *Rubrum Scarlatinum,* N.F. Dark, brownish red, odorless powder. Practically insoluble in water and slightly soluble in alcohol, acetone or benzene; soluble in oils, fats, phenol, chloroform, and warm petrolatum.

Scarlet Red Ointment, *Unguentum Rubri Scarlatini,* N.F. Scarlet red (5%) in olive oil, wool fat, and petrolatum.

Scarlet Red Sulfonate, N.N.R. This differs from scarlet red in that it is the sodium salt of azobenzenedisulfonic acid azobetanaphthol. It is used as indicated for scarlet red.

Acridine Dyes

The acridine dyes, because they are mostly yellow, have been termed "flavines." The most representative members of this group are acriflavine and proflavine. These dyes possess marked antiseptic and germicidal properties and are employed in a number of pathologic conditions.

It is reported these dyes are free from toxic or irritant action on living tissues and do not appreciably inhibit the phagocytic action

of the leukocytes. Acroflavine appears to possess a specific bactericidal action on the gonococcus, an action greater than that of proflavine, but slower.

PREPARATIONS

Acriflavine, *Acriflavina*, N.F. (Acriflavine Base, Neutral Acriflavine). Chlorine (about 14.5 per cent). Antiseptic, especially against the gonococcus; also in wounds and inflamed mucous membranes. *Dosage:* For application to wounds, solution 1:1,000; for irrigation, in solution of from 1:500 to 1:10,000.

Proflavine Dihydrochloride, *Proflavinae Dihydrochloridum*, N.F. $C_{13}H_{11}N_3.2HCl.2H_2O$. Orange-red to brown-red; odorless crystals which are affected by light. Soluble in water (1 in 10). *Caution:* Proflavine dihydrochloride solutions should be dispensed in light-resistant containers and should be discarded when they become turbid. *Dosage:* Solutions of from 1:10,000 to 1:1,000 may be employed for the irrigation of wounds; the higher dilutions are preferable to minimize local irritation when large quantities are to be used.

Triphenylmethane (Rosaniline) Dyes

The triphenylmethane dyes are basic dyes which are effective against Gram-positive organisms. The group includes gentian violet, crystal violet, brilliant green and acid and basic fuchsin. Gentian violet is of greatest importance in medicine.

Gentian Violet. Gentian violet is bactericidal in water and even more so in the presence of serums. It is bacteriostatic against the majority of Gram-positive bacteria and selective between these and the majority of the Gram-negative.

Locally, it is employed as a 1:1,000 aqueous solution in the bladder, urethra, and colon. A 1 per cent solution is used in the mouth for thrush; it is also used in throat infections, in empyema and arthritis. A 1 per cent aqueous solution applied as a spray or swab every two hours is useful in burns. It forms a firm but pliable protection, and is antiseptic and analgesic. In the treatment of *impetigo contagiosa* gentian violet is painted on the lesions in a 1 to 2 per cent aqueous solution.

Orally it is used in the treatment of pinworms, etc. (see Anthelmintics). Intravenously, it has been employed in encephalitis, septicemia, etc., but this use has been abandoned.

PREPARATIONS

Methylrosaniline Chloride, *Methylrosanilinae Chloridum*, U.S.P. (Gentian Violet, Methyl Violet, Crystal Violet). Hexamethylpararosaniline chloride, usually mixed with pentamethylpararosaniline chloride and tetramethylpararosaniline chloride.

Methylrosaniline Chloride Jelly, *Gelatum Methylrosanilinae Chloridi*, N.F. (Gentian Violet Jelly). Contains methylrosaniline chloride 1 per cent in a jelly composed of glycerin and tragacanth with exsiccated sodium phosphate, eugenol, eucalyptol, methyl and propyl parahydroxybenzoate in distilled water.

Methylrosaniline Chloride Solution, *Liquor Methylrosanilini chloridi*, N.F. (Gentian Violet Solution, Crystal Violet Solution). Methylrosaniline chloride (1 per cent) and alcohol (10 per cent) in water. Alcohol content about 9 per cent.

Fluorescein Dyes

Fluorescein and merbromin (mercurochrome) are two fluorescein dyes of medical importance. Merbromin is discussed under the antiseptic mercury compounds.

Fluorescein is chemically related to the phenolphthalein dyes, being a combination of resorcinol with phthalic anhydride. It is an orange-red powder insoluble in water.

Ophthalmologic Use.—A solution of sodium salt of fluorescein is formed by dissolving 2 Gm. of fluorescein and 3 Gm. of sodium bicarbonate in sufficient water to make 100 cc. This solution is used for the diagnosis of corneal lesions and the detection of minute foreign bodies embedded in the cornea. When applied to the cornea only those portions deprived of epithelium are stained. Ulcerated areas are stained green; foreign bodies appear surrounded by a green ring; and loss of substance in the conjunctiva is indicated by a yellow stain.

Preparation

Fluorescein Sodium, *Fluoresceinum Sodicum*, U.S.P.

Phenolphthalein Dyes

The phenolphthalein dyes are used mainly as diagnostic agents, with the exception of phenolphthalein, which is used in medicine as a cathartic. Iodophthalein sodium, phenolsulfonphthalein, and sulfobromophthalein sodium will be discussed.

Iodophthalein Sodium, U.S.P., is a blue-violet powder freely soluble in water (1 in 7) and slightly soluble in alcohol. It is used for roentgenologic examination of the gall bladder. *Dosage:* For each 10 kilograms of body weight: oral 0.5 Gm.; intravenous, 0.3 Gm. (U.S.P.). (See N.N.R. for details.)

Phenolsulfonphthalein, U.S.P. (Phenol Red), is a crystalline powder; stable in air, very slightly soluble in water (1 to 1,300) and slightly soluble in alcohol (1 in 350).

It is used for determining the functional activity of the kidney. Excretions begin five to ten minutes after intramuscular or intravenous injections in the normal person, but are delayed in the presence of deficient functional activity; the degree of this functional deficiency may be estimated by the proportionate amount excreted in two hours. (See N.N.R.)

Preparation

Phenolsulfonphthalein Injection, *Injectio Phenolsulfonphthaleini*, U.S.P. A sterile solution of phenolsulfonphthalein in isotonic sodium chloride solution made with water for injection and rendered soluble with sodium bicarbonate or sodium hydroxide. *Dosage:* Diagnostic; intravenous or intramuscular, 6 mg. phenolsulfonphthalein (U.S.P.). The usual ampule size contains 6 mg. in 1 cc.

Sulfobromophthalein Sodium, U.S.P., is a white crystalline powder soluble in water and insoluble in alcohol. It is used as a liver function test, the dosage being 2 mg. per kilogram of body weight; 5 per cent solution intravenously. (See N.N.R. for more details.)

Preparation

Sulfobromophthalein Sodium Injection, *Injectio Sulfobromophthaleini Sodici*, U.S.P. (Sulfobromophthalein Sodium Ampules). The

usual size contains 150 mg. in 3 cc. *Dosage:* For each kilogram of body weight, intravenous, 2 mg. sulfobromophthalein sodium (U.S.P.).

Methylene Blue

Methylene blue was the first antiseptic dye to be used medicinally. It was recommended as an intestinal antiseptic and also used as a urinary antiseptic, in both instances being of little value.

Methylene blue is a weak antiseptic, but is more efficient as a bacteriostatic agent. It has been reported to be of special value in the treatment of tuberculosis of the urinary tract.

Actions on Hemoglobin.—Methylene blue can oxidize hemoglobin to methemoglobin or again reduce methemoglobin to hemoglobin, according to the circumstances. In severe methemoglobinemia, from nitrate, acetanilide or sulfanilamide, intravenous injections of small doses of methylene blue (1-2 mg. per Kg.) promptly decreases the methemoglobin and increases the oxygen capacity of the blood. The drug may be given orally, 65 to 130 mg. every four hours for the average adult. (A. F. Hartman, 1938.)

As Antidote.—Methylene blue is of some value as an antidote in *cyanide poisoning* (by forming methemoglobin to bind the cyanide) but is inferior to the nitrites. In carbon monoxide poisoning it appears to be not only useless, but toxic. Unfortunately it has been recommended and employed by some for this purpose.

PREPARATION

Methylene Blue, *Methylenum Caeruleum,* U.S.P. (Methylthionine Chloride, U.S.P. XII). $C_{16}H_{18}ClN_3S.3H_2O$. *Dosage:* 0.15 Gm. (2½ grains).

IODINE AND IODINE COMPOUNDS

The germicidal action of iodine was first recorded by Davaine in 1873. The earliest mention of its use in surgery appears in Bryants' *Practice of Surgery* (1884), in which he wrote: "Those who disregard atmospheric germs and highly regard means for purifying wound surfaces, will use antiseptic irrigation of the wound with lotion of iodine, made by adding ten drops of liquor of iodi to the ounce of water. I have employed iodine lotion for years and prefer it to any other."

Iodine-containing compounds, such as *iodoform* and *iodochlorhydroquinoline* (vioform), have been used on wounds in the form of dusting powders. They liberate iodine slowly and lack the irritant action usually attending the application of Strong Iodine Tincture.

Pharmacological Action.—Certain iodine compounds are used for their local irritant and antiseptic effects, which are probably due to the action of free iodine contained in the preparations or liberated from them. Iodine is sparingly soluble in water, although readily soluble in most of the common solvents as well as in aqueous solutions of the iodides. One of the most striking characteristics of iodine is that its effective disinfecting concentration is very similar for all bacteria. The more critical researches have shown that no chemical or physical agent is capable of sterilizing the skin without some degree of irritation. Apparently iodine possesses the necessary qualifications for a skin disinfectant, although it is far from being entirely satisfactory.

Iodine solutions are irritant to mucous membranes. The 3.5 per cent iodine in alcohol is not easily tolerated by the oral mucosa and

some irritation usually follows its use. Rodriguez made a critical study of iodine and other compounds under the adverse conditions found in the oral cavity. He concluded: "Iodine in dilutions of 3.5 per cent, and even 1.75 per cent strength, preferably in glycerin, is an effective germicide from the standpoint of surface disinfection of the oral membrane."

Iodine solutions lack the appeal of many of the new proprietary preparations because of their irritative properties. Nevertheless, iodine continues to remain the standard skin disinfectant, which is evidence of its real value. The claim is made for many of the newer preparations that they retain the germicidal efficiency of iodine without possessing its irritant action. Many of these claims are false; nonirritating iodine compounds frequently possess slight disinfectant action.

Toxicology.—Careful consideration should be given to iodine poisoning. The usual symptoms are pain in the throat and stomach, vomiting, purging, and intense thirst. Giddiness, faintness, and convulsions are commonly present. *Treat* by the administration of sodium thiosulfate (1 to 10 Gm. in water) by mouth. Then lavage with 1 per cent sodium thiosulfate. Administer starch paste. External heat and stimulants may be indicated. · Iodism is treated elsewhere in text.

Therapeutic Uses.—Strong Iodine Tincture, and Strong Iodine Solution (Lugol's Solution) are commonly used preparations. Mixtures of Strong Iodine Tincture with varying amounts of glycerin have given good results when delicate tissues are to be treated. Mixtures of iodine and oil ointments have proved a disappointment as disinfectant preparations. The following iodine preparations are commonly used for antiseptic and disinfectant purposes and for internal purposes.

Strong Iodine Solution

Strong Iodine Solution (Lugol) consists of 4.5 to 5.3 per cent free iodine rendered soluble in water by the presence of 10 per cent potassium iodide. The common incompatabilities are: alkalies, carbonates, alkaloids, vegetable astringents, volatile oils, and starch.

This preparation is an efficient *antiseptic.* Its application is not as painful as is that of the tincture. Two to 5 per cent is used for disinfection on wet or dry skin. As an *alkaloidal antidote* administer orally 1 cc. in a glass of water; follow by gastric lavage. For the *preoperative* treatment of toxic goiter patients, 0.5 cc. is administered one to three times a day for a week prior to operation.

Strong Iodine Tincture

Strong Iodine Tincture contains 6.5 to 7.5 per cent iodine, 5 per cent potassium iodide, 5 per cent distilled water, and 83 to 88 per cent alcohol. The iodide renders the iodine soluble. Its incompatibilities are the same as for the strong solution of iodine. It is used in the treatment of *corneal ulcer* of the simple type. It may be applied by means of a toothpick soaked in the solution and administered cautiously. Strong Iodine Tincture with glycerin is indicated for the treatment of *chronic granular pharyngitis,* and in *acute follicular tonsillitis.* The following prescription may be used:

℞

Strong Iodine Tincture	3.0 cc. (f3¾)
Glycerin	30.0 cc. (f℥j)

M. Sig.: Apply as directed.

In gynecology the tincture may be applied directly to the cervix in *acute gonorrheal endocervicitis.* Diluted solutions are useful as stimulants in the treatment of *ulcers.*

Iodine Tincture

Iodine Tincture contains 2 to 2.4 per cent iodine and about 2.3 per cent sodium iodide in 44 to 50 per cent alcohol. A hydro-alcoholic solution allows deeper iodine penetration and greater efficiency for a given concentration. This preparation may be applied to open wounds with practically no painful aftermath. Delayed drying may account for deeper penetration and greater bactericidal action. The phenol coefficient of this compound is 4.7.

Iodine Dusting Powders

Dusting powders containing iodine in various combinations are used in the treatment of wounds, granulating surfaces, abscess cavities, etc. The beneficial action is based on:

1. The antiseptic action of iodine.
2. Stimulation of phagocytosis.
3. Diminished secretion of wound.

Iodoform, N.F., CHI_3, seems to be the standard preparation. Other insoluble organic iodine compounds have been tried with limited success, although they may be less toxic and avoid the disagreeable odor of iodoform.

Vioform, $C_9H_4N.OH.I.Cl$, an almost odorless substitute for iodoform, may be used as a dusting powder for application to wounds, ulcers, burns, exudative skin eruptions, etc.

PREPARATIONS

Strong Iodine Tincture, *Tinctura Iodi Fortis,* N.F. (Tincture of Iodine, U.S.P. XII). Note: Dispense strong iodine tincture when tincture of iodine U.S.P. XII is ordered.

Iodine Tincture, *Tinctura Iodi,* U.S.P. (Mild Tincture of Iodine, U.S.P. XII. Note: This should not be confused with the 7 per cent tincture of iodine U.S.P. XII, now described as Strong Iodine Tincture N.F.)

Iodine Ointment, *Unguentum Iodi,* N.F. Iodine (4 per cent) and potassium iodide (4 per cent) in glycerin and yellow ointment. Caution: During its manufacture and storage this ointment must not come in contact with metallic utensils or containers (N.F.).

Strong Iodine Solution, *Liquor Iodi Fortis,* U.S.P. (Lugol's Solution). *Dosage:* 0.3 c.c. (U.S.P.), orally in water.

CHLORINE DERIVATIVES

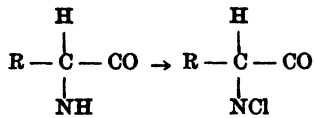
Chlorine, which was discovered by Scheele in 1774, was used soon after its discovery for arresting putrefaction and as a deodorant. It met with almost immediate approval and is now used widely as a chemical disinfectant, especially in the disinfection of questionable water supplies and for rendering sewage less objectionable.

Pharmacological Action of Chlorine Compounds.—Chlorine is a powerful poison to all organic matter, including bacteria. It is a strong irritant to the air passages, capable of producing pulmonary edema and death. In medicine the gas is rarely used, but many derivatives are valuable germicides and bleaching agents.

Mode of Action.—The germicidal power of chlorine is due to oxidation and to direct chlorination. Chlorine combines with hydrogen of water to liberate nascent oxygen, which is a very active germicide:

$$2Cl_2 + 2H_2O \rightarrow 4HCl + O_2$$

It is probable that the germicidal effect of chlorine is due also to the reaction of chlorine with unsaturated components of the germ plasma. Chlorine may directly attack the protein molecule and replace hydrogen in the amino groups yielding chloramines:



GERMICIDAL EFFICENCY OF CHLORINE.—Chlorine in great dilutions is remarkably efficient as a germicide. The phenol coefficient is estimated at 218. In the presence of a heavy suspension of feces, the phenol coefficient is 72.5 at 2° C. and 62 at 20° C. The decrease in the numerical phenol coefficient at the higher temperature does not indicate a decreased activity of the chlorine, but rather that the temperature coefficient of the phenol is much greater than that of the chlorine.

The *efficiency* of chlorine and chlorine compounds is markedly reduced by the presence of excessive amounts of organic matter. The chloramines are least affected by the presence of organic matter. Azochloramid appears to be less affected by the presence of serum than are the other chlorine preparations.

The pH (acidity or alkalinity) is an important factor in determining the germicidal efficiency of chlorine. The germicidal efficiency of chlorine compounds is markedly decreased with increases in the amount of alkali present. The chloramines are also more effective in acid and neutral solutions than in alkaline solutions. In spite of this knowledge attempts continue to be made to combine an alkaline detergent and a chlorine disinfectant. Such products are now being sold to an uninformed public. Chlorine compounds which are made too acid become increasingly corrosive and the less alkaline hypochlorides are, the less stable they are. The problem therefore resolves itself in obtaining that pH (alkalinity) that gives a satisfactory germicidal action and at the same time the maximum stability and the minimum corrosiveness.

Toxicity of Chlorine Compounds.—Chlorine gas and water containing a large amount of chlorine are irritating and corrosive. When water is properly chlorinated the free chlorine is dissipated long before reaching the consumer and no physiological effects occur. The objectionable flavors are not due to chlorine but to the chlorophenols present. When chlorinated lime is swallowed, gastrointestinal irritation follows. The *treatment* is evacuation, followed by the administration of demulcents.

Chlorine gas is of little practical value as an antiseptic. A number of chlorine compounds are available, however, which slowly yield chlorine and can be used for disinfection.

Hypochlorites

Sodium, potassium, and calcium hypochlorites are employed. Solutions of sodium hypochlorite are relatively unstable and should be

freshly prepared. They are employed in the treatment of suppurating wounds, being able to destroy bacteria and dissolve necrotic tissue. Hypochlorites in acid, alkaline, and neutral solutions were used in the treatment of infected wounds but have been largely displaced by antibiotic agents.

PREPARATIONS

Sodium Hypochlorite Solution, *Liquor Sodii Hypochloritis*, U.S.P. About 5 per cent NaClO. Caution: this solution is not suitable for application to wounds. (U.S.P.)

Diluted Sodium Hypochlorite Solution, *Liquor Sodii Hypochloritis Dilutus*, N.F. (Liquor Sodae Chlorinatae Chirurgicalis, Modified Dakin's Solution). NaOCl (about 0.48 per cent). It is an active germicide and antiseptic for infected wounds when used after free incision and cleansing by practically continuous irrigation, as in the Carrel technic. It dissolves necrotic tissues and thus helps to keep the wound clean. It dissolves silk ligatures and loosens catgut, and therefore it may cause secondary hemorrhage. It is practically nontoxic when used externally, but it should not be injected into the peritoneal cavity.

Chlorinated Lime

Chlorinated lime (bleaching powder) is a product consisting of a mixture of calcium hydroxide, calcium chloride, lime, and water. It contains about 30 per cent available chlorine, which is readily liberated, especially in acid solution

$$2\ CaOCl_2 = Ca(OCl)_2 + CaCl_2$$

The calcium hypochlorite furnishes available chlorine while the calcium chloride has no disinfectant value. It is only partially soluble in water or alcohol.

Chlorinated lime is quite irritant, and therefore not well adapted to local application to tissues. It is used as a *deodorant* and *disinfectant* of excreta, as a *bleaching agent*, and in preparation of valuable germicidal chlorinated solutions.

Chloramines

The chloramines are compounds in which chlorine is linked to nitrogen in the form of available chlorine. According to Long, the chloramines are no longer used by surgeons.

PREPARATIONS

Chloramine-T, *Chloramina-T*, N.F. (Chloramine) [$C_6H_4(CH_3)(SO_2N$-$NaCl).3H_2O$]. Soluble in water (1 to 7) and is decomposed by alcohol. Its actions are similar to those of Diluted Sodium Hypochlorite Solution. It is germicidal for infected wounds. Solutions of 1 to 2 per cent are used by continuous irrigation.

Dichloramine-T, *Dichloramina-T*, N.F. (Dichloramine). Paratoluenesulfondichloramide, $C_6H_4.CH_3.SO_2NCl_2$. It contains about 29 per cent of active chlorine. This preparation is insoluble in water but is soluble in paraffin hydrocarbons. It decomposes in air. This preparation exerts a sustained antiseptic action. It is

used in solution in chlorcosane (chlorinated paraffin) in concentration of 2 to 10 per cent for diseases of the nose and throat.

Chlorinated Paraffin, *Paraffinum Chlorinatum,* N. F. (Chlorcosane). Used as a solvent for dichloramine-T which it dissolves to form an 8 per cent solution.

Chloroazodin Compounds

Chloroazodin, *Chloroazodinum,* U.S.P. $C_2H_4Cl_2N_6$. Contains from 37.5 to 39.5 per cent active chlorine (Cl). Bright yellow needles or flakes. It has a faint odor suggestive of chlorine and a slightly burning taste. Solutions of chloroazodin in glycerin and alcohol decompose rapidly on warming, and all solutions of chloroazodin decompose on exposure to light. Very slightly soluble in water, sparingly soluble in alcohol. It is used as a disinfectant to the mucous membranes of the vagina, colon, and rectum in solutions of 1:2,000 in olive oil and for dressing, packing, or irrigating infected wounds and cavities in solutions of 1:3,300 to 1:1,600 in aqueous solution.

Chloroazodin Solution, *Liquor Choloazodini,* U.S.P. Contains, in each 100 cc., 0.26 Gm. of Chloroazodin dissolved in glyceryl triacetate. Caution: Chloroazodin Solution should not come in contact with metal. (U.S.P.) It represents a 1:385 concentration of chloroazodin and is diluted with 7.5 or 3 volumes of water to make 1:3,300 or 1:1,600 aqueous solution, respectively, and with 4 volumes of olive oil to make a 1:2,000 solution in oil.

SPERMATOCIDES

Spermatocides are chemical agents used to kill or immobilize spermatozoa before they gain access to the uterus. It is essential that contraceptive preparations should possess certain properties—they should be effective and they should be nontoxic; and, of course, the esthetic properties of contraceptive preparations are worthy of consideration.

Spermatocidal Drugs. Vehicles.—The esthetic and chemical properties of contraceptive preparations are determined, to a large extent, by the vehicle used for the incorporation of the spermatocidal agent. Jellies (water soluble), suppositories, powders, tablets, and aqueous solutions are usually employed as vehicles and forms of administration.

Jellies are most commonly used for the incorporation of drugs. Most of the spermatocidal jellies contain wetting agents which are strong hydrophilic compounds. The effectiveness of wetting agents is based on their power of reducing surface tension and lowering interfacial tension between solid and solvent, thus permitting rapid dispersion and penetration of the spermatocidal agent.

The spermatocidal drugs generally used include acids, aluminum salts, hexylresorcinol, phenylmercuric acetate, oxyquinolin benzoate, and others. The cheapest and most effective agents are the acids. Lactic acid, and citric acid are effective in about 1 per cent concentrations. The aluminum salts, such as potassium aluminum sulfate, are active by virtue of their ability to precipitate proteins. Hexylresorcinol is effective and harmless. Oxyquinoline sulfate is effective and commonly used.

Glycerite of starch is used as a vehicle in many instances. Frequently, vegetable gums such as gum of tragacanth, gum acacia, gum

bassora, gum Karayo, and others are employed because glycerite of starch is quite irritating to some individuals.

Spermatocidal drugs may be incorporated in suppositories such as cocoa butter and gelatin. Obviously, only those spermatocidal drugs which are miscible with suppository bases can be employed. Cocoa butter has the disadvantage of not mixing with solutions of water-soluble agents, and furthermore cocoa butter does not mix readily with vaginal secretions.

Since some drugs incorporated in cocoa butter and similar fats are not available for absorption or local activity, water-miscible bases have been developed. "Monolene" or the stearic acid ester of α-propylene glycol, containing one-half per cent of either sodium or ethanolamine stearate, is used as an emulsifying agent. This base is smooth and not greasy to touch. The base may be used with either oil-soluble or water-soluble drugs and readily permits transfer of the drugs to the site of action.

Powders may be used as vehicles for spermatocidal drugs. Starch and gum arabic are the most common. The drugs employed include boric acid, tannic acid, zinc sulfate, and others. These drugs are finely powdered, incorporated in the vehicle, and administered by a vaginal insufflator or atomizer.

Boric acid and oxyquinoline sulfate are often incorporated in effervescent tablets and used for contraceptive purposes. The evolution of carbon dioxide from the effervescent mixture is thought to form sufficient foam to delay passage of the spermatozoa mechanically and thus allow the active drug a longer period of time to act.

Simple water solutions of spermatocidal drugs administered by douche are effective if promptly and properly used. Tampons soaked in the spermatocidal agent and placed in the vagina near the cervix are a simple and effective contraceptive procedure.

INDUSTRIAL SKIN CLEANSERS

Personal cleanliness is one of the most important preventatives of occupational dermatitis. Detergents remove dirt in various manners. Soap emulsifies oils, the alkali liberated when soap dissolves acts as a grease solvent, soap also acts as a lubricant and allows dirt to be rubbed away, and finally, the hydrolysis of soap forms colloidal acid soap, which in turn forms colloidal adsorption compounds with the dirt.

Alkali (such as sodium silicate, trisodium phosphate, etc.) is often added to soap to increase the free alkali content; water softeners—sodium hexametophosphate, and sodium tetraphosphate—are often added. Wetting agents are added to assist in the detergent action.

Wetting agents lower surface tension of liquids, enabling them to spread over the surface and penetrate the pores. They also enable the solution to penetrate oily and waxy films, making the dirt more easily removable. The molecule of wetting agents is composed of two parts—one part attaches itself to the water molecule and the other to the oil molecule. In this manner the wetting agent brings together the otherwise immiscible water and oil molecules.

The principal synthetic wetting agents are: the long chain alcohol sulfonates, i.e., Duponal; the alkyl aryl sulfonates, i.e., Santomerse; the alkyl naphthalene sulfonates, i.e., Alkanol; sodium salts of the higher sulfosuccinates, i.e., Aerosol.

An industrial cleanser should be soluble in water, should remove fats and oils, should not extract fats from the skin, and should not be hard or irritant. The following is a typical example:

℞

Neutral toilet soap	30
Colloidal clay (bentonite)	30
Santomerse	10
Lanolin	5
Perfume	q.s.

For soap- or alkali-sensitive workers:

Santomerse (or other detergent)	20
Lanolin	3
Colloidal clay	76
Perfume	q.s.

Liquid form:

Neutral sulfonated castor oil	97
Santomerse or Duponal	2
Castor oil	1

DETERGENTS

The detergents include the common soaps and the synthetic detergents. Simple soaps are excellent detergents when in aqueous solution. However, water must be considered the real cleansing agent, while soap, in lowering the surface tension of the water, assists in wetting the surface to be cleansed. Agitation loosens the dirt, grease and oil are dispersed, and the suds carries the waste away in the rinsing process.

Soaps

Soaps are prepared by saponifying fats or oils with alkalies. The consistency of the soap depends on the predominating acid and the alkali used. Soaps soften water by removing the calcium and forming the insoluble calcium soaps. Soaps are used for the manufacture of pills, liniments, and tooth powders.

Preparations

Hard Soap, *Sapo Durus*, U.S.P., B.P. (Soda Soap).

Medicinal Soft Soap, *Sapo Mollis Medicinalis*, U.S.P., B.P. (Green Soap). Prepared from vegetable oil, oleic acid, glycerin, and potassium hydroxide.

Camphor and Soap Liniment, *Linimentum Camphorae et Saponis*, U.S.P. Hard Soap (6%), camphor (4.5%) in rosemary oil, alcohol and water. Absolute alcohol content about 64 per cent. *Linimentum Saponis*, B.P., soap liniment and about 4% camphor.

Soft Soap Liniment, *Linimentum Saponis Mollis*, U.S.P. (Tincture of Green Soap). Soft soap (65%) and lavender oil in alcohol (30%).

Synthetic Detergents

The most effective synthetic detergents are the cationic compounds (common soaps are anionic) such as benzalkonium chloride (Zephiran chloride), Phemerol chloride, and cetyl pyridinum chloride.

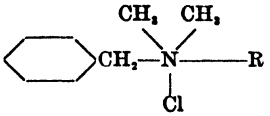
These compounds are readily soluble in water and their aqueous preparations are strongly antiseptic against both Gram-positive and Gram-negative bacteria, and for most nonsporulating bacteria and

fungi. They are, in general, more effective against Gram-positive than against Gram-negative organisms. They have a low surface tension and emulsify readily. Synthetic detergents are nonirritating and relatively nontoxic.

Mode of Action.—These compounds differ in their activity for other antiseptics. One explanation of their action is that they interfere with the membrane equilibrium of the bacteria essential for its normal metabolism, and thus causes its destruction or inhibits its reproduction (Baker, 1941). The activity may be due, in part, to their surface and cation activities (Tice and Pressman, 1945).

Benzalkonium Chloride
(Zephiran Chloride)

Benzalkonium chloride, U.S.P., is a mixture of high molecular, alkyl-dimethyl-benzyl-ammonium chlorides. The chemical structure is



in which R represents alkyl radicals ranging from C_8H_{17} to $C_{18}H_{37}$, as contained in the corresponding fatty acids of coconut oil. It is freely soluble in water, acetone, and alcohol, insoluble in ether, and sparingly soluble in benzene.

Pharmacological Action.—Solutions of benzalkonium chloride possess a low surface tension, a property which enhances its penetrating ability. It also possesses excellent detergent, emulsifying, keratolytic, and emollient properties.

Benzalkonium chloride solution possesses an antiseptic and germicidal action on bacterial organisms and fungi even in low concentration. The action is relatively nonselective. It has been shown to be especially active against hemolytic streptococci, pneumococci and staphylococci.

Toxicology.—Benzalkonium chloride is of low toxicity and nonpoisonous. It is also relatively nonirritating to skin and mucous membranes.

Therapeutic Uses.—Because of the efficiency of benzalkonium chloride as a disinfectant, coupled with its nontoxic and nonirritating properties, it is indicated in many phases of medicine and surgery where skin and mucous membrane antisepsis is required.

A 1:1,000 solution is indicated for use on skin preparatory to surgery. A 1:2,000 solution is useful for the disinfection of skin and mucous membranes in obstetrical and gynecological procedures. For bladder and urethral irrigations an aqueous solution of 1:20,000 is recommended. Benzalkonium chloride aqueous solution, 1:2,000 to 1:3,000, has been found to be nonirritating to the conjunctiva.

For disinfection of superficial wounds or traumatic injuries, a 1:1,000 tincture (50 per cent alcohol, 10 per cent acetone) has been recommended. For the ear, nose, and throat aqueous solutions from 1:1,000 to 1:10,000 concentration may be used. The tincture in 1:1,000 strength is indicated for various skin infections including pyoderma, folliculitis, impetigo, furunculosis, and other infections.

Preparations

Benzalkonium Chloride, *Benzalkonii Chloridum*, U.S.P. (Alkyldimethylbenzylammonium Chloride). An amorphous powder mixture of alkyl dimethyl-benzylammonium chlorides used for the preparation of the official solution.

Benzalkonium Chloride Solution, *Liquor Benzalkonii Chloridi*, U.S.P. *Dosage:* Dilutions of 1:1,000 may be used on the unbroken skin; 1:5,000 for denuded areas and mucous membranes of the eye or vagina; 1:20,000 for irrigation of the urinary tract.

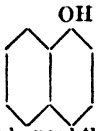
Phemerol Chloride (N.N.R.) is also a dimethyl benzylammonium chloride, with properties and uses quite similar to those described for benzalkonium chloride. *Tincture Phemerol Chloride* 1:500 and *Solution Phemerol Chloride* 1:1,000 (aqueous) are proposed as general purpose germicides and antiseptics.

Cetyl-pyridinum Chloride (Cecpyrn), not official, is similar to the above preparations. Its aqueous solutions are acid.

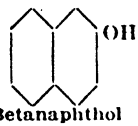
MISCELLANEOUS ANTISEPTICS

Betanaphthol

Naphthol ($C_{10}H_7OH$) is a crystalline, antiseptic substance occurring in coal tar, but usually prepared from naphthalene. It occurs in two forms: *alphanaphthol* and *betanaphthol.*



Alphanaphthol



Betanaphthol

Alphanaphthol is thought to be more antiseptic and also more toxic than betanaphthol. The beta- form, which is several times as germicidal as phenol, is the form used in medicine. It is a colorless or whitish crystalline powder slightly soluble in water (1:1,000), soluble in alcohol (1:8), and in oils.

Action and Uses.—Betanaphthol is an antiseptic and a parasiticide. It is rapidly absorbed from the intestinal tract. After absorption, a portion is broken down but the remainder is excreted by the kidney, partly oxidized to betanaphthoquinone and partly conjugated with glycuronic acid. Betanaphthol first stimulates and then depresses the central nervous system. Large doses depress the heart.

Toxicology.—If absorbed in large amounts it tends to destroy red blood cells and may cause nephritis. It may even produce changes in the retina and cause opacity of the lens. In case of poisoning, treatment consists of stomach lavage followed by the administration of saline cathartics. Since the drug is fat soluble, castor and other oils should be avoided.

The drug may be used *internally* for *diarrhea, intestinal indigestion, typhoid fever,* and for the treatment of *intestinal flukes.* Internally, it is usually administered in capsules and followed by a saline purge. *Externally,* it may be used in the form of ointment, 1 to 10 per cent, for various *skin diseases,* as scabies, ringworm, psoriasis, seborrhea, etc. As an antiseptic, 1:1,000 aqueous solutions are recommended.

In the treatment of scabies:

℞

Betanaphthol
Precipitated Sulfur ----------āā 2.00 Gm. (3ss)
Petrolatum ----------q.s. ad 30.00 Gm. (℥j)

M. Sig.: Apply as directed.

PREPARATION

Betanaphthol, *Betanaphthol*, U.S.P., B.P. *Dosage:* 0.12 Gm. (2 grains).

Ichthammol

Ichthammol, or ammonium ichthosulfonate (introduced as ichthyol) is obtained by the destructive distillation of a bituminous shale of Tyrol. This shale, which contains the fossil remains of fish, is an oil tar containing about 10 per cent sulfur. It is soluble in water and partly soluble in alcohol.

Action and Uses.—It is thought to possess anodyne, antigonorrheal, and antiseptic action, and has been recommended for *phthisis, rheumatism, nephritis, gonorrhea,* and for various *skin diseases.* There is no indication for its internal use.

The *skin diseases* for which it is used are acne, seborrheic conditions, eczema, dermatitis, erysipelas, furunculosis, and psoriasis. Its use in these conditions is based on its penetrating and feebly antiseptic properties. In erysipelas a 10 to 20 per cent ichthammol in lanolin (excellent adhesiveness) is used for its analgesic effect. Unna attributes its action to albumin precipitation.

It is generally used in the form of an ointment, 10 to 50 per cent, or it may be mixed with light petrolatum. It is now used mainly on antiseptic and absorbent tampons for *catarrh* of the *uterus* and *adnexa.*

Compounds of ichthammol with albumin (ichthalbin) and with formaldehyde (ichthoform) have been prepared for internal administration. Although their odor and taste have been improved, the rationale of their use is in question.

For psoriasis:

℞

Salicylic Acid	3.0 Gm. (gr.xlv)
Chrysarobin	6.0 Gm. (℥iss)
Ichthammol	6.0 Gm. (℥iss)
Petrolatum q.s. ad	120.0 Gm. (℥iv)

Make an ointment.

Sig.: Apply to affected areas as directed.

PREPARATIONS

Ichthammol, *Ichthammol,* N.F., B.P. (Ammonium Ichthosulfonate). It yields 2.5 per cent of ammonia, not more than 8 per cent of ammonium sulfate, and not less than 10 per cent of total sulfur. *Dosage:* 0.2 Gm. (3 grains).

Ichthammol Ointment, *Unguentum Ichthammolis,* N.F. Ichthammol (10%) in wool fat and petrolatum.

Benzyl Benzoate

The introduction of benzyl benzoate is an important advance in the treatment of scabies, and it is particularly valuable where large numbers are infected. The ease and speed with which the application can be carried out, the absence of unpleasant effects, the rapidity of cure and the almost immediate relief from itching makes it a very satisfactory remedy. (I. F. Mackenzie, 1941.)

Benzyl benzoate is an oily liquid, insoluble in water and glycerin. It is not used internally. The main therapeutic use is in *scabies.*

Various procedures have been recommended. The following is satisfactory.

Procedure:

Hot bath (soap and water).
Dry skin and apply Benzyl Benzoate Lotion, U.S.P., over entire body.
Repeat application over badly affected parts at once.
Put on previously worn clothing.
Repeat bath and application second day with clean underwear.
At end of second day put on clean clothing and change bedding.

PREPARATIONS

Benzyl Benzoate, *Benzylis Benzoas*, U.S.P. $C_{14}H_{12}O_2$. Contains not less than 99 per cent.

Benzyl Benzoate Lotion, *Lotio Benzylis Benzoatis*, U.S.P. Contains approximately 28 per cent of benzyl benzoate with triethanolamine and oleic acid in water. *Dosage:* Applied topically, undiluted.

Saponated Benzyl Benzoate, *Benzylis Benzoas Saponatus*, U.S.P. Contains approximately 102 per cent of benzyl benzoate with triethanolamine 2 per cent and oleic acid 8 per cent.

Resorcinol

Resorcinol, "Resorcin," a meta-dihydroxyphenol, occurring as colorless, needle-shaped crystals or as a powder, is very soluble in alcohol (1:0.9), and in water (1:0.9). It is related to the other dihydroxyphenols, pyrocatechin, and hydroquinone. Pyrocatechin and hydroquinone are little used in medicine.

Pharmacological Action.—Resorcinol is antiseptic, antipyretic, and antipruritic. It is *absorbed* from the skin and gastrointestinal tract, and is excreted in the urine in combination with sulfuric and glycuronic acids. It has an antiseptic efficiency equal to that of phenol but is less irritant and caustic. Prolonged use is inadvisable because it forms methemoglobin and may result in collapse. A dose of 10 grains may cause vertigo, dizziness, and salivation.

Therapeutic Uses.—Resorcinol is employed externally in *skin diseases*, and sometimes internally in *gastric fermentation* and in diarrhea. It is no longer used internally as an antifermentative. When employed internally it is best given in a solution and well diluted. Externally it is used both in solution and in ointments. It is employed as a 5 to 20 per cent ointment in psoriasis. It is used also in lupus, favus, herpes tonsurans, as a scalp wash for dandruff, and in various forms of eczema. Solutions of from 1 to 3 per cent, when applied externally, are astringent, and in concentrations of from 10 to 20 per cent they produce exfoliation of the epidermis. CAUTION: It discolors blond or auburn hair a greenish tinge. Citric acid removes skin discoloration.

For Dandruff (Richard L. Sutton, Jr.).

℞

Resorcinol Monoacetate	8.00 Gm.	(℥ij)
Mercury Hydrochloride	0.06 Gm.	(gr.j)
Alcohol (60%) q.s.	250.00 cc.	(f℥viij)

M. Sig.: Apply as directed.

Resorcinol Monoacetate, $C_6H_4(OH).(OOCCH_3)$, the monoacetic ester of resorcinol, is similar to that of resorcinol, but milder and more lasting because of the gradual liberation of resorcinol. It is a viscous, lemon

yellow liquid, soluble in alcohol, acetone, and in many organic solvents. It is sparingly soluble in water.

Resorcinol monoacetate is used in the treatment of acne, sycosis, and particularly in the treatment of alopecia and seborrhea. It is applied in ointments of from 5 to 20 per cent and in acetone solution. For scalp lotions, alcoholic solutions of from 3 to 5 per cent are indicated.

PREPARATIONS

Resorcinol, *Resorcinol*, U.S.P., B.P. *Dosage:* 0.125 Gm. (2 grains).
Strong Resorcinol Paste, *Pasta Resorcinolis Fortis*, N.F. (Lassar's Stronger Resorcinol Paste). Resorcinol (20%), zinc oxide (20%), starch and light liquid petrolatum.
Resorcinol Monoacetate, *Resorcinolis Monoacetas*, N.F.

Hexylresorcinol

Hexylresorcinol, $C_6H_3(OH)_2C_6H_{13}$, is a pale yellow liquid or a crystalline solid with a pungent odor and disagreeable taste. It is almost insoluble in water; readily soluble in alcohol and in fixed oils.

Action and Uses.—Hexylresorcinol is an antiseptic, germicide, and anthelmintic. (See Anthelmintics, Chap. VIII.) Some of its bactericidal action is due to its surface-tension-lowering ability. The presence of organic matter tends to decrease its germicidal action. In aqueous solution it is employed as a general antiseptic. It is marketed as a 1:1,000 solution in glycerin and water. Occasionally some individuals exhibit sensitivity to its local application.

PREPARATION

Hexylresorcinol, *Hexylresorcinol*, U.S.P. *Dosage:* Anthelmintic, 1 Gm. (15 grains).

Sulfur

Sulfur is a yellow powder, of slight odor, and acid taste. It is insoluble in water, nearly insoluble in alcohol, slightly soluble in oils and fat solvents, and freely soluble in carbon disulfide.

The use of sulfur and sulfur fumes in attempts to control the spread of infection antedates history. In the Odyssey, Ulysses used sulfur fumes "to free the air of its poison and to purify this palace." Hippocrates used sulfur as an antidote against plague.

Pharmacological Action.—Sulfur has been used for a variety of purposes, but its chief use is as a fungicide and for the treatment of skin conditions.

Mode of Action.—Sulfur itself is not toxic to bacteria, but must be converted to some other form to be active. The fungicidal activity has been attributed to the formation of hydrogen sulfide (H_2S) and also to the formation of pentathionic acid ($H_2S_5O_6$). Both of these substances possess germicidal and fungicidal properties. Sulfur also possesses keratolytic and parasiticidal action.

Therapeutic Uses.—***Internally,*** solutions of colloidal sulfur have been administered parenterally in the treatment of *arthritis*. Evidence for its usefulness and lack of toxicity is lacking. Sulfur-in-oil is a useful adjunct in the treatment of dementia praecox.

Externally, sulfur is employed extensively in the treatment of parasitic skin diseases. It is frequently used in ointments. Precipitated sulfur is preferred, due to its fine state of division and its freedom from odor and taste.

Sulfur ointment, consisting of 15 per cent precipitated sulfur in wool fat, white petrolatum and yellow wax, is a reducing agent, astringent, and irritant. It is an effective *antiscabious agent.* It should be applied at night after a hot bath. Thomas states that the following prescription is most efficient for the treatment of *scabies:* 10 per cent for adults, 5 per cent for children and 2.5 per cent for infants. The potassium carbonate helps to soften the epidermis.

The prescription is:

℞

Precipitated Sulfur	3.0 Gm.	(gr.xlv)
Potassium Carbonate	3.0 Gm.	(gr.xlv)
Petrolatum	30.0 Gm.	(℥j)

Mix and make an ointment.

Sig.: Apply freely with rubbing after hot bath morning and evening on three successive days.

Patients should be forbidden to reapply the sulfur ointment without medical consultation, as a sulfur dermatitis may result.

Acne rosacea responds well to treatment of Camphor-Sulfur (Darier), especially if there is considerable pustulation. It must be remembered that some rosacea patients cannot tolerate sulfur lotions, and Darier's sulfur ichthyol paste should be used instead.

℞

Precipitated Sulfur	10.0 Gm.	(3iiss)
Camphor Spirit	20.0 cc.	(f3v)
Glycerin	5.0 cc.	(f3i½)
Rose Water		
Water āā	45.0 cc.	(f℥iss)

M. Sig.: Apply to face with cotton pledget at night.

For the treatment of *dermatomycosis* a sulfur-salicylic ointment of the following composition is recommended:

℞

Precipitated Sulfur	1.2 Gm.	(gr.xx)
Salicylic Acid	1.8 Gm.	(3ss)
Boric Acid	2.0 Gm.	(3ss)
Rose Water Ointment q.s. ad	60.0 Gm.	(℥ij)

Mix and make an ointment.

Sig.: Apply as directed.

This ointment is useful in the treatment of *mycotic* infection of the skin, alone or in combination with iodine. It may be used daily in *tinea versicolor,* and will clear up the condition if persevered in. It may be used twice a day on alternate days in *ringworm* of the feet.

Wilkinson's Ointment (Compound Sulfur Ointment) is useful in the treatment of borderline cases of psoriasis and in chronic seborrheic eczema. In chronic eczema it must be used with caution.

Preparations

Precipitated Sulfur, *Sulfur Praecipitatum,* U.S.P., B.P. Made by precipitating a solution of calcium sulfide with hydrochloric acid. *Dosage:* 4 Gm. (60 grains).

Sulfur Ointment, *Unguentum Sulfuris,* U.S.P. Precipitated sulfur (15%) in wool fat, and white ointment. B.P. (10%).

Sublimed Sulfur, *Sulfur Sublimatum,* U.S.P., B.P. *Dosage:* 4 Gm. (60 grains).

Compound Sulfur Ointment, *Unguentum Sulfuris Compositum*, N.F. (Wilkinson's ointment). Sublimed sulfur (15%), juniper tar (15%), and precipitated calcium carbonate in soft soap and solid petroxoline.

Sulfurated Potash

Sulfurated potash is a potassium polysulfide and thiosulfate mixture, soluble in water (1:2). It contains not less than 12.8 per cent sulfur combined as sulfide.

Action and Uses.—In moist air, ointment, or solution, it gives off H_2S which may be partially masked by the addition of a volatile oil. It is used for its astringency to dry up moist *eczema*. Its alkalinity makes it useful as a keratolytic agent in psoriasis.

It is employed externally for various skin diseases, such as *psoriasis, scabies,* and *ringworm*. It is used in ointments, lotions, and baths either alone or with other substances. Its chief use in pharmacy is in making White Lotion, N.F.

PREPARATIONS

Sulfurated Potash, *Potassa Sulfurata*, N.F., B.P. Chiefly polysulfides and thiosulfate.

White Lotion, *Lotio Alba*, N.F. Zinc sulfate and sulfurated potash (each 4%) in distilled water. NOTE: The Lotion should be freshly prepared and shaken thoroughly before dispensing.

Dichloro-diphenyl-trichloroethane

(DDT)

Dichloro-diphenyl-trichloroethane (DDT) was synthesized by Othmar Zeitler, 1874. It was introduced as an insecticide by Geigy of Basel. It is a fine powder of faint floral odor, insoluble in water but soluble in many organic solvents. It is rather inert chemically, does not volatilize to any extent, and readily adheres to surfaces.

DDT rates high in destroying domestic flies, mosquitoes, fleas, ticks, bedbugs, lice, etc. Due to its high insecticide activity it is effective in controlling the spread of such diseases as dysentery, dengue, filariasis, malaria, typhus, and others.

This drug can be absorbed from the respiratory and alimentary tracts, and from oily solutions through the skin. After fatal doses in animals it is found mostly in the perirenal fat, and some in the liver, spleen, muscle, brain, blood, and bile. It is not found in the urine, and that in the feces may be unabsorbed.

Toxicology.—DDT is relatively nontoxic for man. Occasional contact is not harmful, but large doses produce serious toxic symptoms in animals.

Clinical symptoms in mild cases include nausea, vomiting, and sore throat for several days (Smith, 1946). Fatal poisoning in a child occurred from ingestion of 150 mg. per Kg.

Treatment.—If swallowed, lavage the stomach and give saline cathartics. Phenobarbital may be given for nervous manifestations.

Therapeutic Uses.—In *scabies* DDT increases the effectiveness of benzyl benzoate. The Army found the following mixture effective.

℞	Per Cent
Benzyl Benzoate	10
DDT	1
Procaine Hydrochloride	2
Ethyl Alcohol	q.s.

Procedure: Patient is given shower and sprayed from chin to toes with above mixture. The patient puts on clean clothes and is allowed no bath until the next day. The next day he is sprayed again and is instructed not to bathe for twenty-four hours. This treatment is reported to be effective in 97 per cent of the cases.

Head Louse Infestation.—Cowan, 1947, reported that a dust of 10 per cent DDT and 90 per cent pyrophyllite is most effective in treating this condition. In the same concentration, DDT is used with great effectiveness against *pubic lice* and against *body lice.* For body lice it is sprinkled upon the clothing.

Nitrofurazone

Nitrofurazone, 5-nitro 2-furaldehyde semicarbazone is a synthetic antibacterial substance advanced by Dodd and Stillman, 1946.

This preparation was introduced under the trade name Furacin. It is inhibitory to bacteria in 1:200,000 concentrations and bactericidal in 1:50,000. It is not essentially fungicidal. It acts against both Gram-positive and Gram-negative bacteria, and is effective in the presence of serum, blood, and other body fluids.

The drug is relatively nontoxic. Man tolerates 2 Gm. daily for long periods of time. Occasionally, symptoms of nausea may appear.

Nitrofurazone is used for a soluble dressing in concentration of 0.2 per cent in carbowax and propylene glycol, liquefying at body temperature and miscible with water. A 0.5 per cent solution is used for a topical solution.

References

Chick, H.: The Theory of Disinfection, A System of Bacteriology, London, 1930, Medical Research Council.

Dakin and Dunham: A Handbook of Antiseptics, New York, 1917, The Macmillan Co.

Davison, F. R.: Detoxifying, Diffusing, Germicidal and Surface Tension Depressing Properties of Soaps, J. Infect. Dis. **43**: 292, 1928.

Davison, F. R.: A Manual of Toxicology, New York, 1939, Paul B. Hoeber, Inc.

Dodd, M. C., and Stillman, W. B.: The In Vitro Bacteriostatic Action of Some Simple Furan Derivatives, J. Pharmacol & Exper. Therap. **82**: 11, 1944.

Downing, J. G., Hanson, M. C., and Lamb, M.: Use of 5-nitro-2-furaldehyde Semicarbazone in Dermatology, J. A. M. A. **133**: 299, 1947.

Dunn, C. G.: Antiseptic and Germicidal Properties of Alkyl-Benzyl-Ammonium Chlorides, Am. J. Hyg. **26**: 46, 1937.

Garrod, L. P.: Principles and Practice of Local Chemotherapy, Brit. M. Bull. **4**: 275, 1946.

Hunter, A. C.: The Evaluation of Antiseptics, J. A. M. A. **121**: 25, 1943.

Marshall, M. S.: Applied Medical Bacteriology, Philadelphia, 1948, Lea & Febiger.

Martin, G. J.: Acridine Antiseptics, Medicine **23**: 79, 1944.

McCulloch, E. C.: Disinfection and Sterilization, Philadelphia, 1945, Lea & Febiger.

Medical Uses of Soap—A Symposium, Philadelphia, 1945, J. B. Lippincott Co.

Organic Mercurial Compounds as Bactericidal Agents (Council report), J. A. M. A. **115**: 2083, 1940.

Rideal, S., and Rideal, E. E.: Chemical Disinfection and Sterilization, London, 1921, E. Arnold & Co.

Stearn, A. E., and Stearn, E. W.: Chemical Mechanism of Bacterial Behavior, J. Bacteriol. 9: 491, 1924.

Topley, W. W. C., and Wilson, G. S.: The Principles of Bacteriology and Immunity, Baltimore, 1929, William Wood & Co.

Walter, C. W.: Aseptic Treatment of Wounds, New York, 1948, The Macmillan Co.

Zinsser, Hans, and Bayne-Jones, S. A.: Textbook of Bacteriology New York, 1939, D. Appleton-Century Co.

CHAPTER VIII

ANTISEPTICS, DISINFECTANTS, AND ANTI-INFECTIVES

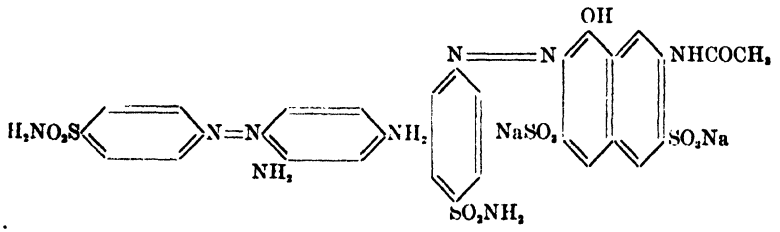
II. ANTI-INFECTIVES

SULFONAMIDES

The development of sulfonamide therapy represents one of the most dramatic and successful achievements in medicine. The sulfonamide drugs quickly passed through the developmental stage and now hold a position of highest importance among our chemotherapeutic agents.

Historical.—Unfortunately, space will allow only a brief recitation of the fascinating history associated with the origin of these compounds. As early as 1908, Gelmo synthesized the compound sulfanilamide (para-amino-benzene-sulfonamide), $NH_2C_6H_4H_2NSO_2$.

He knew nothing of its therapeutic properties which were to be seriously exploited a quarter of a century later. In the following year, 1909, Hörlein stated that, according to Domagk, these dyes possessed bactericidal action on hemolytic septicemia in mice. Ten years later Heidelberger and Jacobs stated again that some of the azosulfamido compounds which they were studying appeared bactericidal in vitro.



Prontosil

Neoprontosil
(Prontosil-Soluble)

In 1932, Mietzsch and Klarer obtained a patent on a substance called prontosil. Later in the same year Mietzsch and Klarer, in association with Domagk, obtained a patent on the substance known as prontosil-soluble. That same year Domagk demonstrated that mice could be protected against fatal doses of streptococci with prontosil, but it was not until 1935 that he published a report on his epoch-making discovery. A few months later Tréfouëls and associates pointed out that para-amino-benzene-sulfonamide (sulfanilamide) was apparently the active part of the molecule with which Domagk worked. This amazing discovery opened the way for extensive experimental and clinical studies.

In 1936 Colebrook and Kenny presented conclusive evidence that prontosil was effective in human streptococcic infections and later they proved that it was of value in the treatment of puerperal sepsis. Other English workers (Buttle and associates) confirmed this work and, furthermore, they were able to protect mice against meningococcic infections with this compound.

Later in 1936 Perrin H. Long and his associate, Eleanor A. Bliss, reported on extensive experimental and clinical studies in this country. E. K. Marshall, Jr., and his co-workers have also contributed outstanding work relative to the sulfonamide compounds. Various investigators have developed and experimented with many new derivatives. Some do not appear to have any real advantage, while others are of definite value and have been introduced clinically.

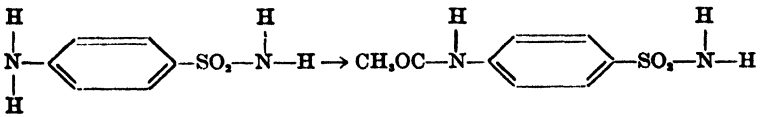
Pharmacological Action.—For the intelligent use of the sulfonamide drugs it is essential for the physician to have an accurate knowledge of their pharmacology. A knowledge of factors concerned with their rate of absorption, degree of conjugation, ability to diffuse, and rate of excretion is vital to successive therapy. Besides an understanding of the pharmacological action of these drugs, it is also essential to understand their mode of action.

Absorption and Excretion.—Most sulfonamide drugs are absorbed more or less readily from the gastrointestinal tract, the speed varying with the compound. *Rectal absorption* is poor, but systemic effects may be obtained with solutions containing two or three times the oral dose. Absorption takes place to some degree wherever the compounds are applied, as skin, mucous membranes, peritoneal cavity, and when given intramuscularly.

Excretion occurs chiefly in the urine, partly free, partly conjugated, varying with the compound used. The rapid rate of excretion, the relatively large amounts involved, and the low solubility, attend to favor precipitation of microcrystals of these drugs in the kidney tubules. In some instances the tubules are actually blocked, resulting in kidney damage, anuria, and finally death.

Distribution.—Once absorbed, these compounds are notable for their distribution throughout all the tissues and body fluids in concentration closely approaching that in the blood. Minor exceptions to this are the poor penetration of sulfathiazole into the spinal fluid and the higher concentration of sulfapyridine found in the liver. It is evident that the sulfonamides circulate in a diffusible state, unattached to the body proteins, a condition ideal for penetration in bacteria. It is interesting that the tissues show a lack of tolerance to these drugs and there is a tendency to produce irritating effects when applied locally. The diffusive mechanisms of the body are not appreciably affected.

Drugs excreted in the urine are partly free and partly acetylated. A part is destroyed in the body and a small amount is temporarily fixed in the liver and kidneys. Chemical change is usually acetylation resulting in the formation of an acetylsulfonamide. The following equation represents the conjugation of sulfanilamide:



free sulfanilamide **conjugated or acetylated sulfanilamide**

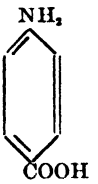
Acetylation is of clinical importance because the acetyl derivative is without clinical effect, yet its solubility in urine may vary from the original compound. Acetylsulfadiazine is more soluble in urine than diazine; on the other hand, acetylsulfathiazole is less soluble than sulfathiazole.

***Mode of Action.*—It is now generally agreed that the primary action of the sulfonamide drugs is one of *bacteriostasis*, that is, they cause a diminution in the rate of growth of the bacteria, probably by inhibition of certain respiratory enzymes. They apparently exert**

this antibacterial effect by interfering with the normal metabolism of the bacterial cell. However, if the drug is present in sufficiently high concentrations, as occurs following local application of the drugs, an actual *bactericidal effect* may be noted on susceptible microorganisms. There is some evidence that a secondary factor, mainly a *phagocytosing effect*, constitutes an important mechanism in eliminating the infection.

Para-aminobenzoic Acid.—Competitive interference with the utilization of para-aminobenzoic acid by the bacteria has been considered another fundamental mechanism. Woods, in 1940, discovered that p-aminobenzoic acid was the substance in bacterial cultures which was capable of neutralizing the effect of sulfonamides. The similarity in structure between the sulfonamides and p-aminobenzoic acid gave a clue to a possible mechanism of action.

Sulfonamide



p-aminobenzoic acid

Para-aminobenzoic acid is believed to be the essential substance necessary for normal cell metabolism. The presence of sulfanilamide or one of its derivatives in the media would block the reaction utilizing p-aminobenzoic acid and thus exert its bacteriostatic action.

Toxicology.—Every physician who uses the sulfonamide drugs should become acquainted with their toxic manifestations.

The toxic effects of the sulfonamide drugs follow a general pattern for the whole group with some differences between the individual drugs. Fortunately, the number of fatal responses is relatively small when compared to the widespread use of these compounds.

Toxic manifestations may be divided into two groups: (1) Those reactions common to all the sulfonamides and which are due to direct poisoning of certain systems in the patient. These reactions may be of minor importance or of a serious nature. (2) The second deals with *sensitivity*. The sulfonamide drugs may sensitize the tissues of patients, and following a subsequent administration more or less severe toxic reactions may occur.

Minor Toxic Reactions.—Nausea and *vomiting* are commonly associated with sulfonamide therapy. The reaction is not due to gastric irritation but is the result of an effect on the central nervous system. Sulfapyridine, sulfanilamide, sulfathiazole, and the diazines are the chief offenders, in the order named. *Cyanosis* is an alarming manifestation following sulfonamide therapy, but it clears up rapidly when the drug is discontinued. It is due primarily to methemoglobin formation or to the temporary formation of some other blood pigment in the red blood cells. Cyanosis rarely occurs with sulfathiazole or the diazines but is extremely common with sulfanilamide therapy. *Dizziness*, mental lapses, lack of coordination, toxic psychoses, etc., are common during sulfanilamide and sulfapyridine therapy, but are relatively rare during sulfathiazole and diazine therapy.

Other toxic manifestations such as microscopic hematuria, crystalluria, mild anemia, stomatitis, and swollen joints are usually of a

mild nature and may not require stopping administration of the drug. If anemia or jaundice is caused by the disease which is being treated, do not withdraw the drug.

Serious Toxic Reactions.—Drug fever is a common toxic reaction associated with sulfonamide therapy, especially with sulfathiazole. It probably appears as the result of a sensitization of the patient. The diazines are the least liable to produce this toxic reaction.

Skin rashes of various types, with and without fever, may result from sulfonamide therapy, especially with sulfathiazole. The diazines rarely produce this condition.

Sensitization of the individual is an important etiologic factor. Photosensitization is also important. Skin rashes may be of little consequence, but in some instances they may progress to severe and even fatal conclusion, even though therapy has been discontinued.

Anemias may occur and may be serious or of little consequence. Mild manifestations of hemolytic anemia are quite common during sulfanilamide or sulfapyridine therapy. Probably no permanent damage results. Deaths have been reported in some instances when the offending drug has not been discontinued. *Hepatitis* is rare but has been reported during sulfonamide therapy. In fatal cases a picture similar to that seen in acute yellow atrophy has been reported.

Agranulocytosis generally occurs when treatment is continued beyond the twelfth day. This toxic reaction is responsible for the majority of fatalities from sulfonamide therapy. Apparently it is not based on any special sensitization of the tissues. Sulfapyridine is the greatest offender, while sulfathiazole or the diazines rarely cause this condition.

Peripheral neuritis may occur, and it is interesting that it usually occurs in patients receiving sulfonamide derivatives containing *methyl* groups. The offenders have been dimethyl sulfanilyl sulfanilamide, monomethyl sulfanilyl sulfanilamide, and sulfamethyl-thiazole. Sulfamerazine does not produce this reaction.

A survey (Long, 1948) indicates that incidence of serious reactions (acute hemolytic anemia, agranulocytosis, drug fever, hematuria, leukopenia, toxic hepatitis, etc.) with the four most common drugs is as follows:

	PER CENT
Sulfathiazole	18.6
Sulfapyridine	15.9
Sulfanilamide	11.9
Sulfadiazine	6.5

The frequency of fatal sulfonamide toxicity makes it necessary to consider all possible measures useful in reducing the reactions. Emphasis should be placed on early diagnosis and early treatment. Early recognition of serious toxic symptoms, followed by prompt cessation of drug therapy and forced fluids is of considerable importance. Symptomatic treatment may also save some patients. *The frequency of sulfonamide toxicity makes it necessary to consider whether the beneficial results of sulfonamide therapy are sufficient to justify the risk of serious toxic reactions.*

All patients taking sulfonamides should be seen daily, if possible, and examined for pallor, rash, and mouth lesions. If they are taking large doses of sulfadiazine, sulfathiazole, sulfamerazine, or sulfapyrazine, the urine should be examined directly for crystals, and microscopically for red blood cells if crystals are present. A hemoglobin estimation and a white blood cell count should be made at least once a week.

It is desirable that sulfonamide blood content balance should be frequently checked in order to maintain a level adequate for therapeutic effects without incurring unnecessary toxic manifestations. A method by Bratton and Marshall may be found in J. Biol. Chem. 128: 537, 1939.

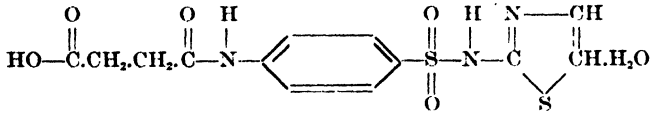
The antidote for sulfanilamide or any of its derivatives is water, and it should be administered by mouth or by intravenous injection of physiological saline with glucose. Force fluids to 5,000 cc. to wash out the offending agent and the toxic symptoms will subside.

Sensitivity.—Some of the reactions occur on the basis of *hypersensitivity* of the patient to the drug. Such sensitivity to the drug may exist even though there is no history of the drug ever having been administered. Occasionally a person becomes sensitive to one or more drugs following use; a number of patients may even show a sensitivity to all the sulfonamide drugs. Sulfathiazole shows a marked tendency to sensitize, sulfanilamide a moderate tendency, while sulfapyridine and sulfadiazine show but a slight tendency. The physician may test a drug sensitivity by administering a small oral dose (1.5 to 4.5 grains) and observe the patient for ten to twelve hours for such reactions as nausea and vomiting, severe headache, fever, and rash.

THE INDIVIDUAL SULFONAMIDES

Succinylsulfathiazole

Succinylsulfathiazole occurs as a white crystalline, almost tasteless powder, very slightly soluble in water, soluble in dilute alkali. The formula is:



This compound resembles sulfathiazole, but little is absorbed from the intestinal tract. It is used for the treatment of infections of the intestinal tract, and is considered safer than sulfaguanidine. The drug itself possesses little antibacterial action, however, a small amount is slowly hydrolyzed to give free sulfathiazole.

Therapeutic Uses.—It is employed for prophylaxis in intestinal operations, and for the treatment of acute bacillary dysentery, and on carriers of these bacteria. The *dosage* is 0.25 Gm. per kilo of body weight by mouth, followed by a maintenance dose of 0.25 Gm. per kilo daily in six equal portions at four-hour intervals. Postoperative, 0.25 Gm. per kilo daily for one to two weeks.

Bacillary Dysentery.—Usually sulfadiazine, which is highly effective against *Shigella* organisms, is given in an initial dose of 2 to 4 Gm. followed every four to six hours by 1 Gm. Continue treatment for two days after clinical recovery. If stool cultures are still positive, substitute *succinylsulfathiazole* in doses of 2 Gm. four times a day. The latter seems more effective in carrier infections. *Remember* that in very severe cases *antidysenteric serum* may be the treatment of choice.

Preparations

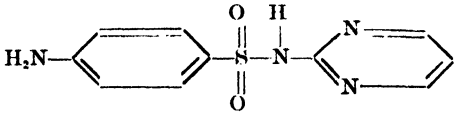
Succinylsulfathiazole, *Succinylsulfathiazolum,* U.S.P. $C_{13}H_{13}N_3O_5S_2.H_2O$.

Succinylsulfathiazole Tablets, *Tabellae Succinylsulfathiazoli,* U.S.P.

Dosage: 2 Gm. (30 grains) succinylsulfathiazole, usually available in tablets containing 0.3 and 0.5 Gm.

Sulfadiazine

Sulfadiazine occurs as a white, nearly odorless powder, stable in air, very slightly soluble in water, and sparingly soluble in alcohol. The structural formula is:



Sulfadiazine is the preferred sulfonamide drug. It is almost as effective as sulfathiazole and its toxic manifestations are appreciably less. It has the advantage of uniform absorption, sustained blood concentration, and relatively low acetylation. As with all the sulfonamides, an initial dose of from 2 to 4 Gm. is necessary, with maintenance doses of 1 Gm. every four to six hours. A blood concentration of 5 to 10 mg. per cent is indicated for mild infections, and one of 15 mg. per cent, or more, is desirable in severe infections.

Absorption of sulfadiazine from the gastrointestinal tract is slower and less complete than with sulfathiazole or sulfanilamide. Sulfadiazine does not pass readily into the body fluids and tissues as does sulfanilamide. It is found in pleural, seminal, prostatic, pericardial, and synovial fluids in from three-fifths to three-quarters of the concentrations found in the blood. It passes readily into the spinal fluid and is found in the bile, sweat, milk, and vitreous and aqueous humors. Probably about 50 per cent of the circulating sulfadiazine is bound to the plasma proteins. It does not penetrate the red blood cells easily. Clinically, it is rarely necessary to determine total sulfadiazine in the blood of a patient as it is not acetylated by the tissues to any great extent. Due to the slow excretion of sulfadiazine in normal individuals, the drug may accumulate in the blood and tissues unless the dosage is adjusted carefully. Less acetylated sulfadiazine is found in the urine than sulfanilamide or sulfathiazole. Sulfadiazine and the conjugated form are not very soluble and tend to precipitate out in the urine. Thus, crystalluria is common, while formation of calculi is less common than with sulfathiazole medication. It is important, however, in sulfadiazine therapy to have an adequate fluid intake.

Toxic reactions are relatively infrequent, occurring in about 8 per cent of the patients. Renal manifestations are the most frequent. Nausea, vomiting, fever, and cyanosis are rare. Hemolytic anemia and agranulocytemia are extremely rare. No acidosis occurs.

Therapeutic Uses.—Sulfadiazine is useful in the treatment of severe hemolytic streptococcic, pneumococcic, meningococci, staphylococcic, and *Escherichia coli* tissue infections. *Dosage:* 2 Gm. (U.S.P.). The initial dosage is ordinarily calculated on the basis of 0.05 to 0.1 Gm. per kilogram of body weight: subsequent doses are usually one-third to one-fourth of the initial dose, given at four-hour intervals, depending on blood sulfadiazine concentration.

Sodium Sulfadiazine has the same therapeutic activities and properties as does sulfadiazine. The soluble sodium salt can be given intravenously when the drug cannot be given orally. The sterilized salt is made up in 5 per cent solution of sterile distilled water for injection in quantities to be checked by blood level determinations to avoid undue high concentrations.

PREPARATIONS

Sulfadiazine, *Sulfadiazinum*, U.S.P. $C_{10}H_{10}N_4O_2S$. *Dosage:* 2 Gm. (30 grains).

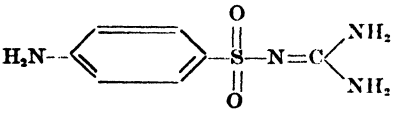
Sulfadiazine Sodium, *Sulfadiazinum Sodicum*, U.S.P. A water-soluble sodium compound of sulfadiazine. *Dosage:* 2 Gm. (30 grains). Intravenous initial dosage is calculated on the same basis as for oral administration, not to exceed a total of 5.0 Gm.; subsequent doses are based on 0.05 Gm. per kilogram of body weight given at twelve-hour intervals.

Sterile Sulfadiazine Sodium, *Sulfadiazinum Sodicum Sterile*, U.S.P. (Sterile Sodium Sulfadiazine). Meets the requirements of the Sterility Tests for Solids, U.S.P. *Dosage:* Intravenous, 2 Gm. (30 grains) adjusted in accordance with the body weight.

Sulfadiazine Tablets, *Tabellae Sulfadiazini*, U.S.P. *Dosage:* 2 Gm. (30 grains) sulfadiazine.

Sulfaguanidine

Sulfaguanidine occurs as a white needle-like crystalline powder. It is nearly odorless and is stable in air. It is slightly soluble in water (1:1,000), sparingly soluble in alcohol, freely soluble in dilute mineral acids, and insoluble in sodium hydroxide. The structural formula is:



The drug is quite soluble in the intestinal contents, but is not readily absorbed so that its blood level rarely exceeds 5 mg. per 100 cc. It is used primarily for local action on the intestinal tract. The drug offers no special advantages over succinylsulfathiazole or sulfathiazole as an intestinal antiseptic.

Toxic reactions are relatively rare. About 10 per cent of the patients have been reported to develop fever. Severe manifestations with rash and hematuria have been reported.

Therapeutic Uses.—It is used as a *prophylaxis* in *colonic surgery*, 0.05 Gm. per Kg. of body weight, every eight hours, day and night for five days before, and seven days after, the operation. It may also be used in the treatment of *bacillary dysentery* but is not the drug of choice.

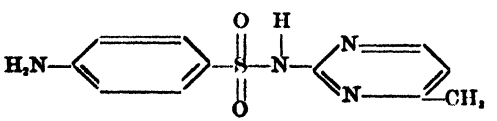
PREPARATIONS

Sulfaguanidine, *Sulfaguanidinum*, U.S.P. $C_7H_{10}N_4O_2S.H_2O$. *Dosage:* 2 Gm. (30 grains) orally.

Sulfaguanidine Tablets, *Tabellae Sulfaguanidini*, U.S.P. *Dosage:* 2 Gm. (30 grains) sulfaguanidine.

Sulfamerazine

Sulfamerazine occurs as a white, odorless, crystalline powder, stable in air and very slightly soluble in water and in alcohol. It is readily soluble in mineral acids and in alkalis. The structural formula is:



Sulfamerazine is a more rapidly and completely absorbed, but more slowly excreted, sulfonamide derivative than sulfadiazine. It is capable of producing effective blood concentration with about one-half the amount required by sulfadiazine. Blood concentrations of 10 to 15 mg. per 100 cc. are recommended.

The low excretion rate of sulfamerazine is explained by the fact that it is reabsorbed by the renal tubules. Sulfamerazine passes into the body fluids and tissues to approximately the same degree as does sulfadiazine. It passes into spinal, pleural, synovial, pericardial, prostatic, seminal, ascitic and edema fluids in about one-half to three-quarters of the concentration noted in the blood. It does not pass into the brain, fat, or bone readily.

Sulfamerazine is not acetylated to any great extent; hence it is usually unnecessary to determine the total concentration of the drug in the blood during treatment. The slower rate of excretion, however, tends to concentration of the drug in the blood, especially in individuals who have decreased renal function.

Toxic Reactions.—It is well tolerated; nausea and vomiting, etc., occur about as frequently as with sulfadiazine. It is less likely to cause crystalluria than sulfadiazine because of its greater solubility in neutral or acid urine.

Therapeutic Uses.—Sulfamerazine is indicated for the same conditions as sulfadiazine. The *dosage:* to keep the blood level at 10 to 15 mg. per 100 cc. starts with an initial dose of 3 or 4 Gm., followed by 1 Gm. every eight hours, continued for seventy-two hours after temperature has returned to normal, unless there are toxic reactions.

PREPARATIONS

Sulfamerazine, *Sulfamerazinum,* U.S.P. *Dosage:* 2 Gm. (30 grains) orally.

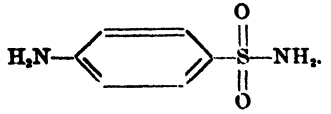
Sulfamerazine Tablets, *Tabellae Sulfamerazini,* U.S.P. *Dosage:* 2 Gm. sulfamerazine (30 grains).

Sulfamerazine Sodium, *Sulfamerazinum Sodicum,* U.S.P. *Dosage:* An initial intravenous dose calculated on the basis of 0.05 Gm. per kilogram of body weight is sufficient to produce a drug concentration of 15 to 20 mg. per hundred cubic centimeters of blood; subsequent doses should be based on 0.25 Gm. per kilogram given at twelve-hour intervals, but oral administration with sulfamerazine should be resumed as early as possible and blood levels checked to avoid a blood concentration in excess of 15 mg. per cent.

Sterile Sulfamerazine Sodium, *Sulfamerazinum Sodicum Sterile,* U.S.P. Meets the requirements of the Sterility Test for Solids, U.S.P. *Dosage:* Intravenous, 2 Gm. (30 grains), adjusted in accordance with the body weight.

Sulfanilamide

Sulfanilamide occurs as white odorless crystals or a crystalline powder. It is soluble in water (1:125) and alcohol (1:37). The structural formula is:



This sulfonamide was one of the first developed as a chemotherapeutic agent; now, it is partly superseded by less toxic derivatives. It is

rarely used today for systemic administration. Saturated aqueous solutions contain approximately 800 mg. per unit at 25° C., while human serum at 37° C. can hold nearly 2,000 mg. per cent in solution.

Sulfanilamide when given by mouth passes readily from the gastrointestinal tract to the body fluids, blood, and tissues. It is evenly distributed to all body tissues and fluids with the exception of the brain, fat, and bone. It passes readily into the spinal, synovial, pericardial, prostatic, and seminal fluids, and also into the vitreous and aqueous humors. About 25 per cent of circulating sulfanilamide is bound by the plasma proteins. The drug penetrates red blood cells easily. About 10 to 20 per cent of circulating sulfanilamide is acetylated (conjugated). It is readily excreted in the urine if kidney function is not impaired. In decreased kidney function care must be exercised to adjust the dose of the drug. Crystalluria and calculi formation are of little concern clinically during sulfanilamide therapy.

Toxic Reactions.—The use of sulfanilamide for local application, originally promoted because of the ease with which high local concentrations could be secured, is gradually falling in disfavor because of the danger of causing sensitization in the host and resistance in the infecting bacteria. Sulfanilamide has a tendency to induce granulocytopenia, therefore administration should be watched carefully between fourteen to forty days after starting treatment.

Many patients receiving sulfanilamide will have symptoms of nervous disturbances such as headache, dizziness, nausea, vomiting, mild depression or elations, and occasionally severe toxic psychoses. Most patients show some cyanosis but this does not require that the drug be stopped. Rashes and drug fever are not infrequent. Acidosis may occur but the routine use of bicarbonate generally prevents this complication. Acute hemolytic anemia and severe leukopenia may occur.

Therapeutic Uses.—It remains the sulfonamide of choice in the treatment of chancroid infections. It is second to sulfadiazine or sulfamerazine in the treatment of aerobic hemolytic streptococcic infections. It probably has little action on staphylococcic infections.

Dosage: For serious infections the dosage of sulfanilamide should be such as to maintain fairly constantly an effective concentration of 10 mg. per 100 cc. of blood. Start administration with 1 Gm. every four hours for adults, totaling 6 Gm. per day; after forty-eight hours this is reduced to 0.5 to 0.66 Gm. every four hours, totaling 3 to 4 Gm. per day. Continue the dosage for several days after clinical recovery; in gonorrhea, for at least two weeks. In milder infections, the daily dosage may be 3 to 4 Gm. from the start. The usual dosage for infants is ⅓ to ½, children ½ to ¾ of the adult dose. Restrict fluids to 4 liters per day. Administer sodium bicarbonate in one-half the quantity of sulfanilamide.

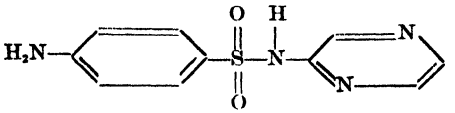
Preparations

Sulfanilamide, ***Sulfanilamidum,*** **U.S.P.** Contains not less than 99 per cent of $C_6H_8O_2N_2S$. *Dosage:* 2 Gm. (30 grains). The initial peroral dose is based on 0.1 Gm. per kilogram of body weight; subsequent doses of one-sixth that amount at four-hour intervals and according to the blood concentration. Subcutaneous doses are the same but administered at six- to eight-hour intervals.

Sulfanilamide Tablets, ***Tabellae Sulfanilamidi,*** **U.S.P.** The usual sizes contain 0.3 Gm. and 0.5 Gm.

Sulfapyrazine

Sulfapyrazine occurs as an odorless, tasteless white crystalline powder. It is soluble in alkaline solutions and in mineral acid solutions. It is slightly soluble in alcohol. The structural formula is:



Sulfapyrazine is an isomer of sulfadiazine. It is absorbed and excreted rather slowly; the blood level rises gradually. Conjugation is relatively small. Its efficiency is similar to that of sulfadiazine.

Toxic Reactions.—Side reactions are much like that for other sulfonamides. Its toxicity is similar to that given for sulfadiazine.

Therapeutic Use.—Sulfapyrazine is probably as effective as sulfadiazine in the treatment of pneumococcal, hemolytic streptococcal, and *B. coli* infections. It appears to be effective against *Shigella paradysenteriae*, even when these fail to respond to other sulfonamides, and in the presence of meningococcic meningitis.

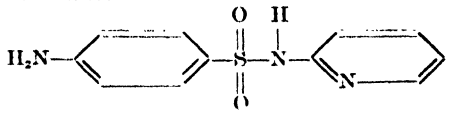
The *dosage* aims to obtain a blood concentration of 5 to 12 mg. per 100 cc. The starting dose is 2 to 4 Gm., followed by 1 Gm. every four to six hours. In severe infections, sulfapyrazine sodium may be given by vein. *Dosage:* Start with 0.05 Gm. per Kg. of body weight administered as a 5 per cent solution. Give subsequent doses of 0.025 Gm. per Kg. at eight- to twelve-hour intervals. The blood concentration of 15 mg. per 100 cc. should not be exceeded.

PREPARATION

Tablets Sulfapyrazine, N.N.R. *Dosage:* 0.5 Gm. (7½ grains).

Sulfapyridine

Sulfapyridine occurs as a white crystalline tasteless powder, sparingly soluble in water, freely soluble in dilute mineral acids and in alkalis. The structural formula is:



This drug is irregularly and poorly absorbed from the intestinal tract. Excretion is slow, and from 4 to 5 days may be required for its complete elimination.

Toxic reactions resemble sulfanilamide in degree and frequency. The incidence of nausea, vomiting, and anemia, however, is greatest with sulfapyridine. Dizziness, headache, and mental reactions may occur. Acidosis does not occur. Many of the more severe toxic manifestations, as described for sulfanilamide, may occur. If toxic manifestations do appear, stop drug and force fluids.

Therapeutic Uses.—Due to water absorption and high frequency of toxic manifestations, sulfapyridine is being rapidly replaced by other sulfonamides. It is more specific than other derivatives for the treatment of dermatitis herpetiformis.

PREPARATIONS

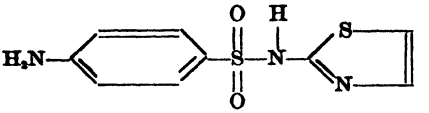
Sulfapyridine, *Sulfapyridinum*, N. F. Contains not less than 99 per cent of $C_{11}H_{11}N_3O_2S$. *Dosage:* 2 Gm. (30 grains).

Sulfapyridine Tablets, *Tabellae Sulfapyridini*, N.F. The usual sizes contain 0.3 Gm. and 0.5 Gm.

Sterile Sulfapyridine Sodium, *Sulfapyridinum Sodicum Sterile*, N.F. (Sterile Sodium Sulfapyridine). Used for the preparation of solutions for intravenous injection. It is made up in concentrations of 5 per cent in sterile distilled water. *Dosage:* 2 Gm. (30 grains).

Sulfathiazole

Sulfathiazole occurs as a white crystalline, tasteless powder, slightly soluble in water and soluble in alcohol (1:200). It is soluble in aqueous alkaline solutions. The structural formula is:



Sulfathiazole is generally rapidly absorbed from the gastrointestinal tract. A single dose may be completely absorbed within three hours; therefore the drug should be administered at intervals of three hours in order to secure adequate concentration in the body fluids. It does not pass readily into the spinal fluid, but is found in about the same concentration as exists in the blood, synovial, pleural, pericardial, ascitic, and edema fluids. About 75 per cent of the circulating sulfathiazole is bound to plasma proteins. About 15 to 30 per cent of the total sulfathiazole in the blood exists in the conjugated form in normal individuals. Sulfathiazole does not penetrate the red blood cells to any great extent. It is excreted in the urine, saliva, milk, and sweat. It is excreted largely in the urine in individuals with normal kidney function. If kidney function is impaired, accumulation in the blood occurs, with resultant toxic manifestations. Acetylsulfathiazole tends to precipitate out in the urine, and it is not uncommon to find calculi formed during sulfathiazole therapy. It is therefore important to administer adequate fluids and to keep the urinary output above normal, otherwise renal damage, evidenced by hematuria, oliguria, or anuria may occur.

Toxic reactions apppear more often than with sulfadiazine. Of all the sulfonamides in use, it leads as a cause of *drug fever* and skin rash and is peculiarly prone to cause scleral injection and damage to the renal epithelium. Nausea, emesis, and dizziness are less frequent than with sulfapyridine. Mental disturbances are more common. Blood changes and hepatitis are rare. Urinary obstructions may occur.

Therapeutic Uses.—Sulfathiazole is probably the sulfonamide of choice in the treatment of gonococcic infections and is considered equal to sulfadiazine in staphylococcic infections. It is more toxic than, and inferior to, sulfadiazine for pneumococcic, meningococcic, and streptococcic infections.

In severe types of infection, due to the above organisms, a concentration of 4 to 6 mg. of the drug per 100 cc. of blood is indicated; less is adequate for gonorrhea.

PREPARATIONS

Sulfathiazole, *Sulfathiazolum*, U.S.P. Contains not less than 99 per cent of $C_9H_9N_3O_2S_2$. *Dosage:* 2 Gm. (30 grains).

Sulfathiazole Tablets, *Tabellae Sulfathiazoli*, U.S.P. The usual size contains 0.3 Gm. and 0.5 Gm.

Sulfathiazole Sodium, *Sulfathiazolum Sodicum,* U.S.P. The sodium salt of sulfathiazole. *Dosage:* 2 Gm. (30 grains), intravenously. Initial doses are computed on the basis of 0.1 Gm. per kilogram of body weight; subsequent doses should be based on 0.05 Gm. per kilogram, administered at six-hour intervals, and not to exceed a blood concentration of "total" drug of 12 milligrams per cent.

Sterile Sulfathiazole Sodium, *Sulfathiazolum Sodicum Sterile,* U.S.P. (Sterile Sodium Sulfathiazole). Meets the requirements of the Sterility Test for Solids, U.S.P. The sterilized equivalent of sulfathiazole sodium used for the preparation of solutions for intravenous injection. *Dosage:* Intravenous, 2 Gm. (30 grains).

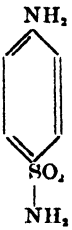
Other Sulfonamides

Sulfamethazine is similar to sulfamerazine in its action but it is more soluble in acid urine. In spite of this increased solubility there is some evidence that kidney damage may occur.

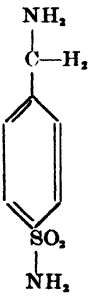
Sulfacetimide possesses properties which qualify it for use as a urinary tract antiseptic. Absorption and excretion are rapid and complete. Since urinary reabsorption is low, high concentrations are easily obtained in the urine with relatively low nontoxic doses.

Intrarenal precipitation does not occur, due to the great solubility of the drug. Furthermore, sulfacetimide is sufficiently soluble in acid urine to permit its use with acidifying agents.

Sulfamylon or hemosulfanilamide appears quite similar in structure to sulfanilamide.



Sulfanilamide



Sulfamylon

Although the structural formulae are quite similar, the antibacterial activity of sulfamylon is quite different. The latter is not affected by the addition of p-aminobenzoic acid to the medium nor is it affected by the presence of pus or necrotic tissue. It has been recommended that it be mixed with nine parts of sulfanilamide and used in the treatment of *Clostridium welchii* and *Cl. septicum* infections, and against resistant strains of streptococcus.

Sulfamylon is contraindicated for systemic administration because of its rapid excretion in the urine. Reports indicate the drug to be relatively nontoxic.

SULFONAMIDE THERAPY

(Including Antibiotics)

The sulfonamides are effective agents against many infectious diseases. Penicillin and streptomycin are the drugs of choice in some diseases; nevertheless, the sulfonamides still remain the most effective agents in others. The sulfonamides are relatively inexpensive, and

may be administered by almost any route. The antibiotics possess, generally, greater activity with negligible toxic effects. Both the sulfa drugs and the antibiotics have a useful and enviable place in modern therapy.

Choice of Sulfonamide.—In general, when systemic therapy is desired, sulfadiazine, sulfathiazole, sulfamerazine, and sulfapyrazine may be used with relatively equal effectiveness. Sulfamerazine is excreted more slowly than sulfadiazine or sulfathiazole, and therefore less frequent administration may be indicated.

More specific recommendations are as follows:

Sulfa Drug	*Infection*
Sulfadiazine	*Streptococcus hemolyticus* Pneumococcus Meningococcus Friedländer's bacillus Influenza bacillus Local application For intravenous use (sodium salt)
Sulfamerazine	Even status for Pneumococcus Meningococcus
Sulfathiazole	Ranks second for all above infections Staphylococcus Gonococcus Colon bacillus
Succinylsulfathiazole	Bacillary dysentery
Sulfaguanidine	Ranks second in Bacillary dysentery
Sulfanilamide	Chancroid

The following outline gives the organisms against which the sulfonamides and penicillin are effective.

I. Infections responsive to both sulfonamide and penicillin:
- Certain Gram-positive and negative cocci
- Hemolytic streptococci
- Pneumococci
- Staphylococci
- Staphylococci viridans
- Meningococcus
- Gonococcus

II. Infections responsive to sulfonamide (not penicillin):
- Gram-negative bacteria
- Colon
- Dysentery
- Hemophilus influenzae
- Friedländer's bacillus
- Ducrey's bacillus
- Plague
- Trachoma
- Follicular conjunctivitis
- Lymphogranuloma venereum
- Pemphigus vulgaris
- Dermatitis herpetiformis
- Actinomycosis
- Lupus erythematosus

} Sulfonamides fairly successful

III. Infections responsive to penicillin (not sulfonamides):
Syphilis
Yaws
Clostridial gas gangrene

Other infections and organisms resistant to the sulfonamides include protozoa parasites, Rickettsiae (typhus and virus), anaerobic and hemolytic B. streptococci, *Brucella melitensis*, common cold, diphtheria, influenza, rabies, rheumatic fever, tuberculosis, tularemia, typhoid, and paratyphoid.

Meningococcus

Both penicillin and the sulfonamides are highly active against meningococci. Because of superior penetration in the central nervous system, a sulfonamide, namely sulfadiazine, is indicated. Give an initial dose of 5 Gm. of sodium sulfadiazine by vein in 500 to 1,000 cc. of sodium lactate solution. As soon as possible, change to oral therapy. Oral dosage is 1 Gm. every four hours accompanied by sodium bicarbonate. Keep blood level between 10 to 15 mg. per 100 cc.

In presence of sulfonamide sensitivity, penicillin may be given in doses of 50,000 units intramuscularly every three hours.

Gonococcus Infections

The sulfonamides were highly effective in gonorrhea, but many resistant strains now prevalent make sulfonamide therapy less reliable. Therapy with *sulfadiazine* or *sulfathiazole* is preferred. The dose of either drug is 1 Gm., four times a day for one week. If there is no discharge and the urine is clear, continue therapy another week with 0.5 Gm. four times a day.

Penicillin is the drug of choice. It is very effective and the dosage is not large. Some recommend 50,000 units intramuscularly every two hours for ten hours. At present, the method of choice for the treatment of acute gonorrhea in the male is penicillin in oil and beeswax (Long, 1948). Administer 300,000 units of crystalline penicillin G in oil and beeswax in outer upper quadrant of buttock.

Ocular Infections

Many ocular infections respond to antibiotics and chemotherapy. Sulfonamides and antibiotics should be used about the eye with extreme caution and only if the indications are absolute.

Urinary Tract Infections (Pyelitis and Pyelonephritis)

The efficiency of sulfonamides vary with the type of infection. They are less effective against *Streptococcus faecalis* than mandelic acid; and less effective than methenamine against *Escherichia coli*. Nevertheless, the sulfonamides are the drugs of choice. The dose of either *sulfathiazole* or *sulfadiazine* is 0.5 to 1 Gm. every four hours. The concentration in the *urine* should reach 75 to 150 mg. per cent and therapy should be continued for four to six days after the urine is sterile.

Penicillin is of little value in urinary tract infection as the usual urinary bacteria are resistant to it. Streptomycin, on the other hand, is effective against infections produced by *E. coli*. However, due to possible toxic effects, it should be reserved for use only if other drugs have failed.

Intestinal Infections

The poorly absorbed sulfonamides, *succinylsulfathiazole* or the less effective *sulfaguanidine* may be used for local antiseptic action in the bowel. Large doses (8 to 16 Gm. a day) are indicated.

Bacillary Dysentery.—Sulfadiazine is highly effective and should be given in an initial dose of 2 to 4 Gm. followed every four to six hours by 1 Gm. Children may be given 0.2 Gm. per Kg. body weight. Continue treatment for two days after clinical recovery. When the stool cultures are still positive at this time, substitute *succinylsulfathiazole* for sulfadiazine in doses of 2 Gm. four times a day.

Local Use of Sulfonamides

Local application of sulfonamides to wounds is of questionable value. Dry sulfonamides produce irritation and sometimes even abscesses. They tend to delay healing and promote excessive scarring. The U. S. War Department discontinued the local use, even on infected wounds (J. A. M. A. 128: 597, 1945).

Wounds

Experience derived from World War II clearly indicates that in wound management sound surgical treatment ranks first, resuscitation of restorative therapy second, and chemotherapy or antibiotic treatment third. Extensive investigations and observations clearly demonstrated that the topical application of crystalline sulfonamides or penicillin as prophylactic agents did not prevent bacterial infection of fresh wounds. Actually such treatment is definitely contraindicated in fresh wounds. No antibacterial agent is available which will effectively sterilize infected pus, blood clots, or dead tissue in wounds.

In minor wounds, experience has demonstrated that chemotherapy or antibiotic treatment is unnecessary and that adequate surgical management is of major importance. In major wounds of soft tissues, in wounds of bony structures, or penetration wounds of the body cavities, systemic or parenteral antibiotic treatment or chemotherapy is indicated to prevent possible infection. For example, in the treatment of compound fractures competent surgical management is of primary importance, and then crystalline penicillin G is the agent of choice. Administer 25,000 units of crystalline penicillin G dissolved in sterile distilled water or an isotonic solution of sodium chloride and give by the intramuscular route, at intervals of three hours day and night. Continue treatment for ten days or until danger of infection seems past. For children, total requirements are based upon 10,000 units per kilogram of weight. Divide this total dose into eight parts and give at intervals of three hours day and night. Continue treatment until danger of infection is past.

Sulfonamides, locally, may be justified in some instances. When indicated, powdered sulfathiazole or sulfadiazine may be applied locally to wound ulcers and serous surfaces, as a 5 per cent ointment to the skin. When used as powder the sulfadiazine or sulfathiazole may be mixed with equal parts of sulfanilamide to prevent clumping, and used in quantities up to 10 Gm.

Skin Infections

Sulfonamide administration to skin might well be limited to pyogenic infections such as *impetigo* and to *chancroidal* infections.

Impetigo.—Sulfathiazole ointment of 5 per cent strength is effective. The most effective treatment is probably *penicillin* ointment.

Chancroidal Infections.—These infections respond dramatically to sulfonamides. Sulfanilamide is preferred as a powder diluted with 20 per cent starch.

Pneumococcus Infections

The sulfonamides are successful in pneumonia, especially in children, for all types of pneumococci. Individual cases showing resistance, however, may require penicillin. Sulfadiazine is preferred for oral use, but sulfathiazole is just as effective but may produce a slightly higher degree of toxicity. The use of the soluble sodium salts may be indicated in starting the treatment if nausea and vomiting interfere with administration.

Moderately Severe Pneumonia.—*Penicillin* may be given intramuscularly in doses of 30,000 to 40,000 units every three hours until the patient's temperature is normal, and then continued at the same dosage for three days longer, omitting the early morning dose.

A possible second choice is sulfadiazine, 4 Gm. initially, followed by 1 Gm. every four hours thereafter until the patient's temperature is normal for two or three days.

Staphylococcus Infections

The staphylococci commonly cause local surface infections (boils, carbuncles, etc.) and also internal or systemic infections (pneumonia, abscesses, endocarditis, etc.) which are more severe.

Local infections should be treated surgically when indicated. Applications of a 5 per cent sulfathiazole ointment may be indicated.

In systemic infections penicillin should be given in large doses by all possible routes and heavy sulfadiazine therapy should also be given at the same time.

Osteomyelitis is an excellent example. This infection is usually caused by staphylococcus, but the infection may be due to streptococcus, pneumococcus, and other bacteria. Penicillin should be administered in doses of 50,000 to 100,000 units intramuscularly every three hours, and continued at this dosage for three weeks or more. When abscess is present, surgical drainage may be necessary in addition to penicillin.

In osteomyelitis caused by streptococcus, pneumococcus, and other bacteria, treatment with streptomycin or the sulfonamides is indicated.

Tuberculosis

Sulfadiazine, sulfamerazine, sulfamethazine, and sulfapyrazine are possibly the only sulfonamides which have any deterring effect on tuberculosis (Smith, 1945). Some of the related sulfones (promin, diasone, and promizole) have a fairly pronounced inhibitory effect on tuberculosis in rabbits and guinea pigs. Streptomycin has a definite retarding effect and at times, apparently, a curative effect on certain types of tuberculosis. (Hinshaw, Mayo Clinic, 1948.)

Prophylactic Use of Sulfonamides

Army and Navy experience indicates that the continuous daily administration of 0.5 Gm. of sulfadiazine decreases the incidence of streptococcus respiratory infections by 50 to 75 per cent (Holbrook, 1944; Coburn, 1944). Billow and Albin, 1946, gave 1 Gm. of sulfadiazine daily to 20,000 soldiers, with a drop of one-third in hospital admissions for *respiratory disease*, a marked decrease of *rheumatic fever* attacks and no cases of *meningitis* occurred. While sulfa drugs are contraindicated in the acute phases, reports indicate that sulfonamides have distinct value in recurrences. Sutliff, 1944, reported six

occurrences in three hundred six treated, while in three hundred and forty-one controls there were seventy recurrences. Penicillin apparently fails to influence the course of *rheumatic fever.*

In *gonorrhea* after three doses of sulfathiazole (2 Gm. each) given to fourteen hundred troops after exposure, reports show there occurred eight cases per thousand per year, while in four thousand untreated there were one hundred seventy-one cases per thousand per year. (Loveless and Denton, 1943.)

Since the advent of the sulfonamides and antibiotics, too much hope has been placed in their use as prophylactics against infection. (Long, 1948.)

Drug Resistance

The fear that microorganisms will become resistant to the agent used for the treatment has been given considerable emphasis. Perrin Long, 1948, expresses his opinion on this subject as follows: "It also seems to be true—*clinical reports to the contrary*—that originally resistant strains or resistant strains induced by treatment have played a minor role in the treatment of *clinical infections* with either the sulfonamides or penicillin."

In streptomycin therapy, however, resistant strains are easily selected out or resistant mutants easily produced. Physicians must bear this in mind when no response is obtained from adequate streptomycin therapy.

Precautions in Sulfonamide Therapy

All authorities agree that daily inspection of patients taking sulfonamides is indicated. The onset of toxic symptoms is usually recognized clinically, with the possible exception of agranulocytosis. Inspection of the skin, mucous membranes, conjunctiva, urine, and feces may be sufficient to diagnose the toxic pattern. A knowledge of the time of appearance and the characteristic toxic symptoms may prepare the physician for early recognition of the condition.

Fever, leucopenia, and oliguria are most frequent with the derivatives of sulfanilamide. Take *temperature* twice daily to guard against fever. *Leucopenia* rarely occurs before the tenth day of treatment; therefore, every effort should be made to end treatment by this time, particularly if the patient is ambulatory. After ten days a close check must be kept on the *white-cell* count with determinations every two days. Oliguria is most apt to occur in the period of intensive therapy. The appearance of red cells or granular casts in the urine should serve as a warning that this toxic reaction is imminent, but the best precaution is to observe the urine output in twelve-hour periods. When this falls below 800 cc., fluids should be forced intensively. Sulfathiazole, particularly, may cause complete anuria without the appearance of hematuria. Crystals of the drug mean nothing in a routine urine examination, since these drugs crystallize at room temperature, but the presence of large numbers of crystals in a freshly voided specimen means that the patient needs either more fluid or a smaller dose.

Drug fever may occur after administration of the sulfonamides has been stopped. This is particularly true of sulfadiazine which is the most slowly excreted, and is to be feared in patients with poor renal function, who rid themselves of any of these drugs very slowly. Sulfathiazole, although it produces toxic reactions more often than does sulfadiazine, is excreted very rapidly, so that if a reaction occurs (except oliguria) it is possible to get rid of the offending drug very quickly. This usually produces prompt recovery from the toxic effects. On the other hand, with sulfadiazine several days are required for its elimination. Because of the possibility of delayed reactions after cessation of therapy,

the white cell count and the patient's condition should be checked three and five days after treatment is discontinued.

It would be wise to maintain an adequate vitamin intake in patients ill with an infection and who are receiving sulfonamide therapy. Long (1941) recommends the following amount of vitamins each day during the course of illness: Vitamin A, 6,000 international units; thiamine chloride, 3 mg.; riboflavin, 3 mg.; nicotinic acid, 50 mg.; ascorbic acid, 100 mg.; vitamin D, 100 to 200 international units.

Routine for Treatment.—

A. Before Administration:
   1. Inquire about previous sulfonamide therapy.
   2. Assess renal function.
   3. Determine hemoglobin level and white cell count.

B. Administration to Ambulatory Patients (Small Doses).
   1. Instruct patient
      a. Name of drug
      b. Importance of regular doses
      c. Importance of adequate fluids and check on output.
      d. Possibility of toxic reactions (report reactions).
      e. Explain danger of slow reaction time, driving car, crossing streets, etc.
   2. a. Physician should see patient daily to take temperature and examine him for jaundice or rash.
      b. Arrange check-up; after ten days see patient three times a week up to six weeks, then weekly as long as drug is given. Check-up should include examination of mucous membranes for pallor, scleras for icterus, skin for rash, temperature. Inquire about nausea and vomiting. Make white cell count; if below 6000 a blood smear should be examined.

C. Administration in Hospital (Large Doses).
   1. Instruct patient and nurse about importance of regular doses.
   2. Measure and record the intake and urine output. Examine urine for gross blood daily, and record N.P.N. at least twice a week.
   3. Observe temperature chart.
   4. Determine hemoglobin every other day.
   5. White cell count three times a week. (Stop drug if white count is below 3500 or the polymorphonuclears are below 50 per cent.)
   6. Examine smear weekly.
   7. Examine physical appearance daily (pallor, skin rash), scleras, jaundice, general appearance and action.

ANTIBIOTICS

Waksman, the discoverer of streptomycin, gives the following definition for antibiotics: "Those chemical substances produced by microorganisms, which have the ability either to inhibit or destroy other microorganisms."

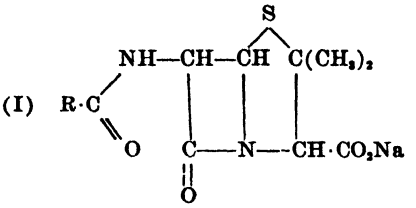
PENICILLIN

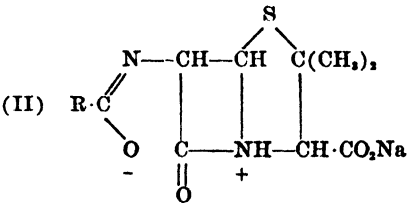
The bacteriostatic action of penicillin was discovered by A. Fleming in 1929. While studying staphylococcus variants, he noted a transparent zone surrounding a mold contaminant of a culture plate of staphylococcus. Believing this clear zone to be evidence of lysis of the bacteria by a substance produced by the mold, he prepared filtrates of broth cultures of this mold and demonstrated their antibacterial activity. Since the mold belonged to the genus *Penicillium*, he adopted the name "penicillin" for the active agent.

The therapeutic application of penicillin was due to the untiring work of Chain, Florey, and their co-workers, 1940. They were able to pro-

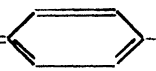
duce stable preparations of penicillin and then were able also to carry on extensive experimental and clinical investigations. The demands of war and the untiring energy of Florey and his associates produced promising clinical results. The synthesis of penicillin has been accomplished by du Vigneaud, Carpenter, and their associates, 1946.

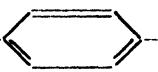
Four varieties of penicillin, designated as F, G, K, and X have been isolated from the same mold. They are esters of a substance which probably have one of the following formulas:





Penicillin F, Δ^2-pentenylpenicillin; R=CH_3—CH_2—CH=CH—CH_2—

Penicillin G, benzylpenicillin; R=  —CH_2—

Penicillin X, *p*-hydroxybenzylpenicillin; R=HO—  —CH_2—

Penicillin K, N-heptylpenicillin; R=CH_3—$(CH_2)_6$—CH_2—

These penicillins have approximately equal bacteriostatic activity in vitro. In vivo, however, penicillin K has very little activity, probably due to an adsorption of penicillin K on serum and tissue proteins. Microorganisms containing penicillin are able to inactivate penicillin.

Many other types of penicillin have been isolated but commercial brands are mostly mixtures of either sodium, potassium, or calcium salts of two or more of the above. Preference should be given to the use of penicillin which contains more than 75 per cent of sodium or potassium salt of crystalline penicillin G.

The penicillins are strong monobasic acids and are therefore employed in the form of alkaline salts. The salts of potassium are too toxic for use; the sodium salts are least toxic. The calcium salt is somewhat less hygroscopic than the sodium salt, and has greater stability. Crystalline preparations of penicillin are odorless and tasteless. Amorphous preparations are yellow and bitter in taste. Only the solid crystalline form may be stored without refrigeration. Aqueous preparations if they are sterile, kept neutral or slightly acid, may be kept for a month after preparation.

Pharmacological Action.—*Mode of Action:* Penicillin probably acts, in part at least, by inhibiting cell division in microorganisms and also by direct destruction. Its action is known to be different from the sulfonamides. Penicillin is not markedly inhibited by the presence of blood, pus, or tissue extracts. Local anesthetic agents do not interfere with its action.

When penicillin is administered by mouth, a part is destroyed by the hydrochloric acid of gastric juice. *Absorption* is excellent from the duodenum and jejunum, but relatively poor from the stomach and also the large intestine. About one-third of the penicillin administered orally is excreted in the urine. Since the liver does not inactivate penicillin, it is difficult to understand why but one-third of the penicillin can be accounted for. Following oral administration maximal concentrations of the antibiotic are attained in thirty to sixty minutes. Since absorption and distribution of the drug is so variable, it is necessary to administer at least five times more penicillin per dose orally than would be given intramuscularly or by vein.

When aqueous solutions of penicillin are administered by *vein,* peak concentrations are reached in the blood in a few minutes, and the blood levels begin to fall. When administered by *muscular injection,* maximal concentrations are reached in from thirty to sixty minutes. Following *subcutaneous injection* peak concentrations are generally reached in about sixty minutes. Following injection by any of the above routes maximal concentrations are soon reached in the blood and if renal function is normal the antibiotic concentration in the blood falls rapidly. Within three or four hours after administration only traces may be found. This is the reason for the usual three-hour schedule recommended for intramuscular administration of penicillin.

Rapid absorption follows administration of penicillin by *inhalation.* Blood concentration curves resemble those observed after intramuscular injection. When penicillin is administered by the intrapleural, intrathecal, or intrapericardial routes, its diffusion in the blood is much slower. Small amounts of the antibiotic may be found in the spinal fluid, pleural fluid, synovial cavities, and pericardial fluid from twelve to twenty-four hours after injection of a single dose. On the other hand, when penicillin is injected in the peritoneal cavity it is rapidly absorbed.

Penicillin is *excreted rapidly*—about 80 per cent of the dose appears in the urine in two hours. After four hours there is less than 5 per cent in the body; therefore, administration must be repeated at short intervals. Penicillin is also excreted in the bile and probably a small amount in the stool. Little, if any, penicillin is excreted in the saliva, sweat, milk, and tears. If renal function is seriously impaired, penicillin will pile up in the blood.

A dose of 50,000 units may produce a blood concentration of 0.5 units per cubic centimeter within a few minutes after injection, and be too low to measure after two or three hours. Concentrations of 0.1 to 0.5 unit are useful therapeutically.

Methods of Administration.—Methods of continuous intravenous or intramuscular infusion are used to maintain blood concentration. The usual method is by intramuscular administration, using aqueous solutions at intervals of two to six hours. Penicillin in peanut oil and beeswax may be administered intramuscularly or subcutaneously. This permits less frequent injections (twelve to twenty-four hours) and still gives quite adequate blood concentration. Other methods to

delay absorption are used; these include application of ice bags, use of a vasoconstrictor such as epinephrine, and admixture of penicillin with plasma proteins.

Many attempts have been made to decrease the rate of penicillin excretion. Diodrast, para-aminobenzoic acid, and other substances have been used to decrease its rate of excretion. Caronamide has been used with considerable success in decreasing penicillin excretion. It acts by competing with penicillin for excretion by the renal tubules and thus decreases the rate of secretion of the latter, and consequently the concentration of the antibiotic in the blood is more easily maintained.

Locally, penicillin is used in solutions and ointments of from 500 to 1,000 units per cubic centimeter or more, and as lozenges or troches in the mouth.

Penicillin may also be given by inhalation for both local and systemic results. When administered as an aerosol, it is rapidly absorbed into the circulation to produce blood levels comparable to those obtained by intramuscular administration.

Penicillin is usually dispensed dry in sterile, rubber-capped bottles, containing 100,000 units. Physiological saline, or other diluent, is added to make solutions from 5,000 to 50,000 units per cubic centimeter for injection.

Toxicology.—Toxic manifestations from penicillin are rather infrequent. To my knowledge no fatalities or very serious toxic manifestations have been reported clinically. The most serious toxic reactions appear to be due to allergic sensitization. This may appear as urticaria, dermatitis, and related disturbances. Systemic allergic reactions are rare. The greater incidence of allergic reactions follow local application. Reactions may reach 10 per cent following local administration as compared to less than 1 per cent after parenteral use. When allergic reactions do happen stop penicillin and treat as for serum sickness.

Intravenous doses have caused fever, chills, nausea, vomiting and even convulsions. *Intrathecal* administration has been followed by headache, vomiting, myelitis and cranial nerve injuries.

Penicillin Resistance.—Bacteria present may be resistant to penicillin, either because they acquired such resistance following therapy or because both sensitive and nonsensitive organisms are already present. In some resistant bacteria, penicillinase is found. Rammelkamp, 1945, states that with the exception of staphylococcus, there are no well-substantiated instances of penicillin resistance acquired during therapy.

Therapeutic Uses.—Penicillin is effective in infections caused by Gram-positive organisms, including *Staphylococcus aureus* and *albus*, *Streptococcus hemolyticus* and *viridans*, pneumococci, clostridia, and *Corynebacterium diphtheriae*. Gonococci and meningococci are also susceptible, but most Gram-negative forms are not affected.

In syphilis, penicillin gives promising results. (See Drugs Used in Treatment of Syphilis.) It also appears to be effective in Vincent's angina, yaws, and relapsing fever.

For the use of penicillin in *streptococcus*, *staphylococcus*, *gonococcus*, and *pneumococcus* infections, see under *Sulfonamide Therapy*.

Gas Gangrene Infections.—Penicillin is probably the drug of choice. Give intramuscularly 50,000 units every three hours. Polyvalent anerobic serum should also be given in amounts up to 100,000 units, intramuscularly, intravenously, and locally around the wound in the course of three to four days.

Pre- and Postoperative Care.—Some surgeons recommend the use of penicillin for preparation and aftercare of their patients. Bacon and Rowe, 1948, recommend that penicillin be employed routinely in doses of 30,000 units every three hours. If contamination is present, the sulfones are used intravenously until they are tolerated by mouth.

Rheumatic Heart Disease.—Penicillin has been tried, and quite successfully, in the treatment of this formerly almost 100 per cent fatal condition. Penicillin has been administered by almost all accepted methods. A daily dose of 500,000 units for a sensitive organism and 1,000,000 units for resistant organisms have been recommended. A treatment period of four to six weeks is suggested. Inadequate dosage is the usual reason for failure.

Penicillin Unit.—The international unit of penicillin is the activity of 0.6 microgram of pure sodium penicillin G.

The assay is generally made by comparing the growth inhibitory effects of the standard and unknown on a penicillin-sensitive organism.

PREPARATIONS

Penicillin Calcium, *Penicillinum Calcicum*, U.S.P. The calcium salt of an antibiotic substance obtained during growth of *Penicillium notatum* Westling or *Penicillium chrysogenum* Thom (Fam. *Aspergillacea*), or produced by any other means. It complies with the requirements of the Federal Food and Drug Administration. *Dosage:* Oral, on a fasting stomach, 300,000 units. Intramuscular, 300,000 units (U.S.P.).

Penicillin Sodium, *Penicillinum Sodicum*, U.S.P. The sodium salt of an antibiotic substance obtained during the growth of *Penicillium notatum* Westling or *Penicillium chrysogenum* Thom (Fan. *Aspergillaceae*), or produced by any other means. It complies with the requirements of the Federal Food and Drug Administration. *Dosage:* Oral, on a fasting stomach, 300,000 units. Intramuscular, 300,000 units (U.S.P.).

Penicillin Dental Cones, *Denticoni Penicillini*, U.S.P. Composed of penicillin calcium and suitable harmless diluents, and it may have sulfonamide compounds added. The cones must comply with Federal regulations and be certified by the Federal Food and Drug Administration. *Dosage:* 1 cone (U.S.P.).

Penicillin Injection in Oil and Wax, *Injectio Penicillini in Olco et Cera*, U.S.P. A sterile suspension of penicillin calcium in a mixture of peanut oil, or sesame oil, in which white wax is dispersed. It meets the requirements of the Federal Food and Drug Administration. *Dosage:* Intramuscular, 300,000 units of penicillin (U.S.P.), usually available in syringe cartridges or vials containing 100,000, 200,000 or 300,000 units per cubic centimeter.

Penicillin Ointment, *Unguentum Penicillini*, U.S.P. Penicillin calcium in an ointment base approved by the Federal Food and Drug Administration.

Penicillin Tablets, *Tabellae Penicillini, U.S.P.*—Penicillin in the form of its calcium or sodium salt in admixture with buffers such as calcium carbonate, anhydrous sodium citrate, and aluminum hydroxide or with other buffers approved by the Federal Food and Drug Administration. *Dosage:* On a fasting stomach, 300,000 units of penicillin (U.S.P.), usually available in tablets containing 50,000 or more units.

Penicillin Troches, *Trochisci Penicillini*, U.S.P.—Penicillin in the form of its calcium or sodium salt, or both, admixed with one or more suitable and harmless diluents, binders, lubricants, masticatory

substances, coloring, and flavoring, approval by the Federal Food and Drug Administration. *Dosage:* One troche (U.S.P.), usually available in troches containing 20,000 units each.

STREPTOMYCIN

Streptomycin is an antibiotic substance produced by certain strains of Streptomyces griseus when grown in suitable media. It was discovered by Waksman in 1944.

Pharmacological Action.—Streptomycin can be administered only by the parenteral route for the treatment of systemic infections. When given by mouth, practically none of it is absorbed and the greater part of it is excreted in the feces. Little or none of the drug is absorbed in the blood following its administration by inhalation.

Following the intravenous injection of streptomycin, maximal concentration appears in the blood almost immediately. When administered intramuscularly, maximal levels are found in the blood in sixty to one hundred and twenty minutes.

Excretion.—Following intramuscular or intravenous injection of streptomycin, its excretion by the kidneys is greatest in the two hours following administration, and within twelve hours from 30 to 60 per cent is excreted in the urine.

Most of the drug is excreted in the urine within twenty-four hours. At present it is not known whether streptomycin is excreted in milk, saliva, sweat, or tears. A small amount is excreted in the bile. If renal function is impaired seriously, the drug will accumulate in the blood and may produce a direct toxic effect on the auditory and vestibular apparatus.

Distribution.—Streptomycin is distributed only in the extracellular fluids. It diffuses slowly into the spinal fluid. It is also found in ascitic fluid and in pleural, synovial, and pericardial effusions, but in concentration less than in blood. The antibiotic passes into fetal blood and amniotic fluid in concentrations about one-half that of maternal blood. Following intramuscular administration, adequate concentrations have been found in aqueous and vitreous humors.

Toxicology.—At the present time streptomycin produces toxic reactions in about 6 per cent of all patients to whom it is given over a considerable period of time. Toxic reactions are more prevalent in patients who have received multiple courses of therapy with this drug.

Deafness is a side reaction of considerable consequence. This reaction occurs usually after the eighth day and is produced by a direct toxic effect of the agent on the nuclei of the eighth nerve. It occurs in about 1 per cent of all patients receiving therapy over a prolonged period of time. Patients in whom prolonged therapy is contemplated should have their hearing tested with an audiometer before therapy and at weekly intervals. If there is a decrease in hearing during treatment, probably streptomycin should be discontinued.

Vestibular dysfunction is a common and often serious toxic reaction associated with streptomycin therapy. This reaction usually appears about the fourth week of therapy but may appear sooner. Usually, the evidences of vestibular dysfunction are of little consequence and may not call for stoppage of the drug. In some patients, however, dizziness becomes severe and vestibular dysfunction may become permanent. The physician must use his judgment and carefully weigh the consequences of continued therapy against the benefits derived from it.

Renal irritation is common, especially in patients with an acid urine. The usual manifestations are casts in the urine, albuminuria, and an

abnormal number of red blood cells in the urinary sediment. If urinary function is normal, treatment is probably continued. However, in cases of decreased renal function great care must be exercised in streptomycin therapy. *Skin eruptions* may occur, usually during the second or third week of treatment. As a rule, they do not indicate discontinuance of treatment. If an exfoliative dermatitis appears, stop treatment at once.

Fever due to sensitivity to the drug may occur and may require discontinuance of the drug in some cases. *Local irritating* effects are often very annoying. *Nausea* and *vomiting* may occur but are usually of little consequence. *Eosinophilia* appears quite often and may indicate some degree of sensitivity.

In a review of the literature of some nine hundred patients treated with streptomycin, eight showed a mild leukopenia, and there was one case of agranulocytosis. In a group of four hundred patients treated with streptomycin, only two showed a serious depression of blood elements (Deyke, Wallace, 1948).

Therapeutic Uses.—Streptomycin is effective particularly against certain infections caused by Gram-negative bacteria and to some extent against the tubercle bacillus. In general, it is the drug of choice for the former when infections are serious and if sulfonamides are ineffective or contraindicated.

Colon Bacillus Infections.—These infections are relatively susceptible to streptomycin and also the sulfonamides. In severe infections both may be administered together. Streptomycin may be given in doses of 0.5 Gm. intramuscularly every three hours.

Influenza Bacillus Infection.—Intensive therapy with streptomycin is indicated in all serious influenza bacillus infsections. Give in doses of 0.5 Gm. intramuscularly every three hours. Children's doses are according to weight. For *meningitis*, streptomycin should be given intrathecally as well as by muscle. The adult dose may be 0.1 Gm. in 10 cc. of saline daily; the infant 25 to 50 mg. daily.

Undulant Fever.—Streptomycin has been reported to be effective in undulant fever (W. W. Spink, 1948). He recommends a combination of sulfadiazine and streptomycin administered in multiple doses over three weeks. At the University of Minnesota he reported seventeen cases out of a total of eighteen were cured by this treatment.

Infant Diarrhea.—Streptomycin is credited, in a Los Angeles hospital, with eliminating deaths from infant diarrhea. No victims were reported during an eight-month period in which it was used. Previously this disease ordinarily killed about 50 per cent of those infected.

Tuberculosis.—Streptomycin is not a cure for this disease but is a most valuable adjunct to the regular and accepted methods of collapse therapy. Levine et al. (1948) reported that in nineteen patients streptomycin therapy caused a decided diminution of toxic symptoms, inhibited spread of disease, and aided resolution of recent infiltrations.

Tularemia.—The use of streptomycin has completely changed the picture of the therapy of this disease as the infection responds well to this drug. One gram, or less, for five days has been found effective. It may be given as 0.25 Gm. intramuscularly four times a day for one week. This treatment is usually sufficient.

Streptomycin is available as the sulfate or hydrochloride in the form of a sterile powder in a rubber stoppered bottle, to which physiological salt solution is added to prepare a solution for administration. One gram contains approximately one million units. Solutions containing 100 to 200 mg. per cubic centimeter are used for intramuscular or subcutaneous injection; 10 to 20 mg. per cubic centimeter for intrathecal

injection; 1 mg. per cubic centimeter for local use; and 50 mg. per cubic centimeter for inhalation.

Streptomycin Unit.—The official unit or "S" unit is defined as the activity of 1 microgram of pure crystalline streptomycin base. Assays are based on the inhibition of growth of a standard strain of *E. coli* as determined by the dilution method. Methods for its detection chemically have been devised. That of Marshall, Blanchard, and Buhle is satisfactory for hospital use.

TYROTHRICIN

Tyrothricin is obtained from a soil bacterium, *Bacillus brevis,* first isolated by Dubos, 1939. It contains at least two active antibiotic substances, *gramicidin* and *tyrocidin,* which are bacteriostatic and bacteriolytic for several Gram-positive organisms. Most of the activity is due probably to gramicidin since tyrocidin is largely inhibited by the presence of serum proteins and cephalin. The bacteriostatic action appears to be due to inhibition of metabolic enzymes of the susceptible bacteria. Some believe the antibacterial properties of gramicidin and tyrocidin to be related to their detergent properties.

The clinical use of tyrothricin is in the experimental stage. It is useful in the treatment of Gram-positive organisms including *Streptococcus hemolyticus, faecalis, pyogenes,* and *Staphylococcus aureus.* It is used only locally in superficial *indolent ulcers,* ulcers, mastoiditis, empyema, and some wound infections. It should be used cautiously in body cavities. Tyrothricin is used in Veterinary Medicine for the treatment of bovine mastitis.

Thyrothricin can be used rationally on superficially infected acne, impetigo, sinusitis, mastoiditis, superficial skin infection, etc.

The use of tyrothricin is limited due to its toxicity, as parenteral administration causes hemolysis of red blood cells. It is systemically dangerous by vein (H. J. Robinson, 1942).

Tyrothricin is marketed as a concentrate or as an alcoholic solution. It may be diluted with isotonic saline so that the solution contains 500 micrograms per cubic centimeter. When using it as local antiseptic, apply a solution containing 0.5 mg. per cubic centimeter (N.N.R.).

POLYMYXIN

In May, 1947, Benedict and Langlykke reported that sterile culture filtrates of *Bacillus polymyxa* inhibited the growth of *Brucella bronchiseptica* in culture. Soon Stansley et al reported (July, 1947) the isolation of an antibiotic substance from *B. polymyxa* which they named "polymyxin."

This new antibiotic is highly active in vitro against certain varieties of Gram-negative bacteria. Its acute toxicity in experimental animals is greater than that of penicillin or streptomycin. The drug is stable against heat and chemical action. After intramuscular injection of the antibiotic, it promptly enters the blood stream, but it does not pass the blood-brain barrier. It is excreted slowly in the urine.

In experimental studies polymyxin appears more effective than streptomycin. The results in various clinical investigations are hopeful. The drug has been used successfully on children with severe burns, whooping cough, and skin diseases associated with secondary infection. It has been tried with apparent success in bubonic plague, Asiatic cholera, undulant fever, bacterial dysentery, typhoid fever, and other intestinal

diseases. One big advantage of polymyxin over other drugs is that the germs it attacks do not apparently develop a resistance to it.

Careful clinical trials of this compound in selected and suitable types of infections must be made before the therapeutic effects of polymyxin can be properly evaluated.

AUREOMYCIN

Aureomycin.—This antibiotic substance has been obtained from a Streptomyces and possesses unusual antibiotic properties. Wright, L. T., et al. (1948) demonstrated its virucidal properties in human beings. Braley and Sanders (1948) reported that aureomycin has definite antibacterial activity against many microorganisms including coccic and bacillary forms and in organisms resistant to penicillin and the sulfonamides. It may be useful in the treatment of infections with rickettsias or with viruses of the psittacosis-lymphogranuloma venereum group, and also in atypical pneumonia (Schoenbach and Bryer, 1949). Aureomycin deserves extended clinical trial.

OTHER ANTIBIOTIC AGENTS

Bacitracin is an antibiotic substance isolated by Johnson, Anker, and Meleny in 1943, from *B. subtilis* cultures. They found that it is neutral, thermostable, and nontoxic on intravenous injection; nonirritating to the conjunctiva, nonhemolytic, and resistant to proteolytic enzymes. When applied locally, its action is not inhibited by pus or microorganisms.

Experimentally it is active in vivo against hemolytic streptococcic infections and mice and gas-gangrene infections in guinea pigs. In vitro it is active against gonococci and meningococci. It possesses bactericidal activity against a large number of Gram-positive organisms.

Promising clinical results (Meleney and Johnson, 1947) have been reported from the local application of bacitracin in surgical infections, especially those of staphylococci and nonhemolytic streptococci which resist penicillin and sulfonamides.

Clavacin (Patulin) is a substance which has been isolated in crystalline form from *Aspergillus clavatus*. It is bactericidal in fairly high dilutions to both Gram-positive and negative bacteria. It is nontoxic following oral or local administration, but highly toxic on intravenous or intramuscular injection. It has been used by nasal installation against colds with questionable results.

Subtilin, another antibiotic obtained from *B. subtilis*, has been effective experimentally against some diseases caused by Gram-positive bacteria. It is apparently nontoxic.

ANTHELMINTICS

Anthelmintics are drugs which are used to kill or remove worms from the intestinal tract. They may be divided into *vermicides*, drugs that kill the parasites, and *vermifuges*, the drugs that cause expulsion only. The results often depend on the size of the dose and on the length of time the drug is held in the gastrointestinal tract.

The following is a list of the helminths which most commonly infest the human intestine and which physicians may be called on to treat:

1. *Platyhelminthes.* A. *Cestodes* (tapeworms): (a) *Taenia saginata* (beef); (b) *Taenia solium* (pork); (c) *Diphyllobothrium latum* (fish); (d) *Hymenolepis nana* (dwarf). B. *Trematodes* (flukes): (a) *Schistosoma haematobium, S. mansoni, S. japonicum;* (b) *Fasciolopsis buski;* (c) *Clonorchis sinensis;* (d) *Paragonimus westermani.*

2. *Nemathelminthes* (Nematodes); 1. Hookworms (Necator and Ancylostoma); 2. Roundworms (Ascaris); 3. Pinworms (Oxyuris); 4. Whipworms (Trichuris); 5. *Strongyloides stercoralis;* 6. *Trichinella spiralis;* 7. *Folaria bancrofti.*

CLINICAL IMPORTANCE.—The *Taenia saginata* does not produce disease. It may produce indigestion, but it does not live, strictly speaking, at the expense of the host. The reverse is true with the *Taenia solium* (pork tapeworm), because the human being may be the intermediate or the definite host in its life cycle. It is important clinically to distinguish between these two. There is a simple method of making the *diagnosis:* Place one of the segments of the worm on a slide and cover by another slide, press together and hold to the light. The genital orifice is visible on the lateral margin, the vaginal portion of the genital tract extending into the body of the worm joined by the two stem branches of the uterus. If there are thirty or more main collateral branches of the uterus per segment, the specimen in question is a nonpathogenic *Taenia saginata;* if there are fifteen or twenty main collateral branches it is the *Taenia solium,* which indicates immediate therapy.

Diphyllobothrium latum was believed for many years to produce anemia, but this impression has been disproved. *Hymenolepis nana* is the most frequent type of tapeworm in the southern states.

Diseases caused by *roundworms* are characterized by different types of therapy from those given diseases caused by flatworms. A definite diagnosis of hookworm infection should be made before subjecting the patient to strenuous hookworm treatment. Infection by the roundworm *Ascaris* may cause serious mechanical damage. These organisms may mass upon the small intestine, giving rise to intestinal obstruction, or migrate into the appendix, common bile duct, or up to the paranasal sinuses. They do not live on the host's tissues. The *pinworm* does not live on the host's tissues but one might say in symbiosis with the host. It is difficult to eradicate. In children, especially, they cause local skin irritation, nervousness, and insomnia. The *whipworm* is rare but may cause definite lesions by burrowing into the mucosa. Symptoms are slight and strenuous therapy is questionable. The *Strongyloides stercoralis* is frequently found in the southern states.

Most parasitic worms are found in the gastrointestinal tract, notable exceptions being the schistosoma, filaria, and trichinella, which are tissue invaders.

Fluke Infestation.—Several varieties of trematode (fluke) infestation in man are known. *Blood Flukes*—three varieties of blood flukes inhabit the circulatory system of man, causing schistosomiasis (bilharziasis). The most common is *Schistosoma haematobium,* characterized by parasitic infestation of the pelvic veins particularly those around the bladder. The symptoms are hematuria, cystitis, and others. The *S. mansoni* causes alimentary symptoms, particularly diarrhea, and later splenomegaly. Like *S. hematobium,* it is widespread in Africa and South America. *S. japonicum* causes hepatomegaly, splenomegaly, and wasting cachexia. It is found in Eastern Asia.

Other flukes include intestinal flukes, e.g., *Fasciolopsis buski,* which may be treated by tetrachloroethylene (same as treatment for hookworm). The liver flukes, e.g., *Clonorchis sinensis* may be treated by antimony (see Stibophen). Gentian violet may also be used—give 60 mg. in capsule form, three times a day for one month. The living flukes, e.g., *Paragonimus westermani,* are difficult to treat. Some recommend the use of emetine as described for *Amebiasis.*

Tartar emetic, stibophen, fuadin, anthiomaline, and other anthelmintics are used in the treatment of fluke infestation.

Trichinosis is an infestation by *Trichinella spiralis*. The larvae enter the body in incompletely cooked meats, migrate usually to the muscles and become encysted after reaching adult form. Fever, prostration and aches are the usual *symptoms*. Treatment is unsatisfactory.

Filariasis.—Several varieties of filarial worms infest man, the most common being *Filaria bancrofti*. The disease is transmitted by mosquitoes. The larvae form grows in the human being to the adult size which may inflame and obstruct the lymphatic system. When the worms mature, they produce microfilariae which serve to infect new mosquitoes. Various antimony compounds including neostibosan have been used in treatment.

The anthelmintics show little specific action on the parasite. Their use is rendered possible because of their slow absorption which permits them to act more vigorously on the parasite than on the host.

The intelligent administration of anthelmintics requires a knowledge of (1) the species involved; (2) the number and location of the parasites; (3) the drug of choice, its indications and contraindications, and (4) the method of determining the therapeutic efficiency of the treatment.

In the choice of a drug we are concerned not merely with the question of which anthelmintic is the most effective, but also with the question of which one is the safest. There is no single satisfactory anthelmintic. Smillie (1939) has stated that "we have been looking for an ideal vermifuge for a long time, but it has never been discovered."

The following is a list of some of the more important anthelmintic drugs and the helminths against which they usually are administered:

Oleoresin of Aspidium (Tapeworm)
Carbon Tetrachloride (Hookworm, Tapeworm)
Tetrachlorethylene (Hookworm, Trichuris, *Trichinella spiralis*)
Hexylresorcinol (Ascarides, Hookworm, Oxyuris, *Hymenolepis nana*)
Oil of Chenopodium (Hookworm, Ascarides)
Gentian Violet (Oxyuris, Strongyloides)
Santonin (Roundworms)
Tartar Emetic (Flukes)
Stibophen (Flukes)
Anthiomaline (Flukes)
Neostibosan (*Filaria bancrofti*)
Miscellaneous Anthelmintics
    Leche de higuerón
    Acranil
    Pelletierine Tannate
    Phenothiazine

Oleoresin of Aspidium

Oleoresin of aspidium is a dark green, thick fluid obtained from the rhizomes of Aspidium or male fern. Aspidium or male fern is found widely distributed throughout the world and has been used as a vermifuge since ancient times. The anthelmintic action resides in several closely related substances, i.e., filicic acid, aspidin, albaspidin, etc. The most important is probably the amorphous filicic acid.

Pharmacological Action.—Aspidium has a strong local irritant action on the gastrointestinal tract. Large doses stimulate the spinal cord. It is a direct cardiac depressant because large doses slow the heart and

weaken the force of contraction. The active principle, filicic acid, probably acts by paralyzing the muscles of the parasite. A small amount of aspidium is absorbed and this is excreted in the urine partially unchanged and partially decomposed.

Toxicology.—Symptoms of toxicity may occur following the administration of therapeutic doses, and large doses are often dangerous. Usually the active constituents of aspidium are not absorbed but if absorption occurs, violent symptoms may ensue. The symptoms of poisoning are colic, diarrhea, headache, dizziness, dyspnea, yellow vision, and temporary blindness. Severe symptoms are characterized by delirium, cramps, syncope, tonic convulsions, and coma. Recovery is slow and often accompanied by permanent blindness. *Treat* the poisoning by administering an evacuant followed by a demulcent. The stomach should be emptied by a non-depressing emetic, such as powdered mustard (a tablespoonful in a cup of warm water). A full dose of magnesium sulfate should be given to flush out the bowel. The patient may be stimulated by heat, strychnine, caffeine, etc. Recovery is slow.

Therapeutic Uses.—Oleoresin of aspidium is a useful drug in the treatment of tapeworms. Castor oil and other fixed oils or fats are contraindicated, as they favor absorption of the toxic drug. Alcohol is prohibited. The usual dose of oleoresin of aspidium for children is 0.5 gram per year of age, but *not* to exceed 5 grams. Even in an adult this dose had better not be exceeded.

The substance is exceedingly bitter and the taste is difficult to disguise. It may be best administered in capsule form. Magath and Brown (Mayo Clinic) use the following prescription:

℞

Aspidium Oleoresin	8.00 Gm.	(3ij)
Acacia	6.00 cc.	(f3iss)
Water q.s. ad	60.00 cc.	(f℥ij)

M. Stir well.

Sig.: As directed by physician.

ADMINISTRATION.—

1. Starvation diet for two days (of questionable value).
2. Saline purge (magnesium sulfate, 15 Gm. in water) twice within first forty-eight hours (of questionable value).
3. Third day: Give oleoresin of aspidium on empty stomach in doses of 2 cc. in capsules at half-hour intervals for three doses. (Total dose 6 cc.)
4. After final dose give capsule containing 2 cc. of spirit of turpentine, followed by a saline purge and two hours later by a large soapsuds enema to ensure complete evacuation of colonic contents.
5. Look for head of worm in stool. If the drug has not been effective, repeat procedure in two or three weeks.

PREPARATIONS

Aspidium, *Aspidium*, U.S.P. (male fern). The rhizome and stipes of European aspidium (male fern) or American aspidium (marginal fern), which have retained their internal green color. Contains not less than 1.5 per cent of crude filicin. *Filix Mas*, B.P., 4-12 Gm. (60-180 grains).

Aspidium Oleoresin, *Oleoresina Aspidii*, U.S.P. *Dosage:* Caution. Single dose, once a day 4 Gm. (60 grains) in capsules or in emulsion.

Carbon Tetrachloride

Carbon tetrachloride (tetrachloromethane, CCl_4) is a clear, colorless liquid, possessing a chloroform-like odor and practically no taste. It is very slightly soluble in water (1:2,000) and miscible with alcohol. It is an effective and relatively cheap remedy for the treatment of hookworms but is considered quite toxic. It soon became apparent, however, that severe liver damage was produced if sufficient amounts of carbon tetrachloride were absorbed. Investigations have shown that toxicity of CCl_4 was reduced if the patient was given a carbohydrate- and calcium-rich diet and was warned to abstain from alchol and fatty foods.

Carbon tetrachloride has been replaced largely by two safer agents, tetrachloroethylene and hexylresorcinol.

Preparation

Carbon Tetrachloride, *Carboneі Tetrachloridum*, N.F. *Dosage:* Caution! As an anthelmintic for adults, single dose, 2.5 cc. Not to be repeated within three weeks.

Tetrachloroethylene

Tetrachloroethylene (carbondichloride, $CCl_2{:}CCl_2$) is a synthetic, chlorinated, aliphatic hydrocarbon of low toxicity and high efficiency, and is the drug of choice for the removal of hookworms. Therapeutic doses are nontoxic. On account of its low solubility in water, there is little absorption from the intestine. It is especially indicated for hookworm infestation. It has been used against other worms with less success. Its use against ascaris is not recommended because of the danger of causing migration of the worms.

Procedure.—Administer from 1 to 3 cc. of the drug, depending on the age of the patient. Children may be given 0.2 cc. for each year of age up to fourteen. Tetrachloroethylene is usually administered in soft gelatin capsules. (Discard broken capsules.) The gastrointestinal tract should be thoroughly emptied before administering the drug. No fats, oils, or alcohol should be given with, or some time after, the administration of tetrachloroethylene, because they promote the absorption of the drug. A dose of tetrachloroethylene should be followed by a saline cathartic of sodium or magnesium sulfate. One dose of tetrachloroethylene is usually sufficient, but if necessary it may be repeated after a period of ten to fourteen days.

Although it may produce slight giddiness and drowsiness, no deaths have been reported from its use in hookworm infection. It is the consensus that tetrachloroethylene is less toxic than carbon tetrachloride (CCl_4) and at least as efficacious. It is important to distinguish tetrachloroethylene (C_2Cl_4) from tetrachlorethane ($C_2H_2Cl_4$), because the latter is a dangerous poison.

Trichinosis.—Treatment for this condition is most unsatisfactory. All the anthelmintics have their advocates. When a mild intestinal upset and low fever can be recognized as the intestinal stage of infestation, the administration of 2.5 cc. of tetrachloroethylene followed in two hours by a purge to remove the worms is recommended (Cutting, 1948). The purge may remove worms before they penetrate the intestinal wall. This treatment is for the early stage only.

Preparation

Tetrachloroethylene, *Tetrachloroaethylenum*, U.S.P. *Dosage:* 3 cc. (45 minims).

Tetrachloroethylene Capsules, *Capsulae Tetrachloroaethyleni*, U.S.P. The usual sizes contain 0.2 cc., 1 cc., and 2.5 cc.

Hexylresorcinol

Hexylresorcinol (1:3 dihydroxy-4-hexylbenzol) was introduced into medicine as a urinary antiseptic by Leonard (1924) and was recommended by Lamson and Ward (1931) as an anthelmintic.

Pharmacological Action.—Hexylresorcinol is an efficient antiseptic. It has a phenol coefficient of 45. Part of its antiseptic action may be due to its great ability to lower surface tension. Following oral ingestion one-third of the drug is *absorbed* and the rest *excreted* unchanged in the feces. The absorbed portion of the drug is excreted by the kidneys in a conjugated form which greatly decreases its action as a urinary antiseptic.

Toxicology.—High concentrations of hexylresorcinol are irritant and damaging to tissues. Oral administration may cause irritation of the mouth and gastrointestinal tract. It has a low systemic toxicity, probably due to its limited absorption.

Therapeutic Uses.—Hexylresorcinol in hard gelatin capsules (single dose, 0.6-1.0 Gm.) is the preparation of choice in ascariasis (Faust, 1941). It is essentially nontoxic, much more efficient than santonin and distinctly safer than oil of chenopodium. Pretreatment and posttreatment saline purgation are indicated.

This drug is also active against hookworm, oxyuris, dwarf tapeworm, and whipworm. Because of its effectiveness against so many varieties of worms, and since it is a drug of low toxicity it is the most valuable single anthelmintic agent. It is particularly useful in the treatment of children and other individuals not able to stand more drastic anthelmintics.

ADMINISTRATION.—

Routine Instructions:

1. Administer in morning before breakfast.
2. Dosage: Children below 6 yr., 0.6 Gm.; for those 6 to 10 yr., 0.8 Gm.; for adults, 1.0 Gm.
3. Two hours later, administer saline cathartic.
4. Food may be taken after 5 hours.
5. May repeat regimen at three-day intervals.

NOTE: Use this procedure for all types of parasites.

PREPARATION

Hexylresorcinol, *Hexylresorcinol*, U.S.P. *Dosage:* Anthelmintic, 1 Gm. (15 grains).

Hexylresorcinol Pills, *Pilulae Hexylresorcinolis*, U.S.P. *Dosage:* 1 Gm. (15 grains).

Chenopodium Oil

Chenopodium oil (Oil of American Wormseed) is a volatile oil distilled with steam from fresh overground parts of the flowering and fruiting plant of *Chenopodium ambrosioides* var. *anthelminticum*. It is an effective anthelmintic against the hookworm, pinworm, and tapeworm. It is more effective against the hookworm and more pleasant to take than thymol. The active constituent is *ascaridol* ($C_{10}H_{16}O_2$) which is present in from 45 to 70 per cent concentration. This compound is 30 per cent more toxic than the whole oil. The oil has the serious disadvantage that different samples vary in toxicity and that it deteriorates with age.

Pharmacological Action.—The drug is *absorbed* chiefly from the small intestine. In therapeutic doses it is *excreted* by the lungs and kidneys over a prolonged period of time and is not readily detected pharmacologically. It is excreted in the urine combined with glycuronic acid.

The drug irritates both skin and mucous membrane; it depresses the circulation and slows and weakens the pulse. The drug paralyzes, but does not kill, the worms which must be eliminated by free purgation.

Toxicology.—Therapeutic doses often produce minor toxic symptoms, especially dizziness and nausea, and sometimes vomiting and deafness. There may follow a deafness lasting for years. Albuminuria and hematuria may occur. The drug is contraindicated in nephritis, organic heart disease, hepatic dysfunction or ulceration of the intestine. It should be administered only under the direct supervision of a physician. Great care should be taken in the use of this drug in the treatment of poorly nourished individuals and in cases of advanced heart and kidney disease; in pregnancy it is contraindicated. Severe intoxication is frequent and is generally attributed to overdosage; a few deaths have been reported from therapeutic doses.

Treatment.—The treatment is mainly symptomatic. Caffeine and strychnine may be used as stimulants, and atropine to check salivation, cramps and respiratory depression.

Therapeutic Uses.—This drug has lately won a high place in the treatment of ascariasis; reports indicate that a single dose will remove from 70 to 100 per cent of the worms. Originally it was employed chiefly for ascarides, but it is now used also in the treatment of hookworm disease, although, because of its toxicity, it has largely been replaced by other drugs.

In the administration of this drug the preliminary starvation and laxative treatment is not necessary. Sometimes a 3 cc. dose is placed in two capsules and given two hours apart, the final dose being followed in two hours by a purge of castor oil. Darling and Smillie found that a dose of 1.5 cc. of the oil removed 90 per cent of the worms and cured 80 per cent of the cases. For treatment of a child give as many drops of the oil on a piece of lump sugar, as the child is years old. Repeat in two hours, then follow in three hours by a castor oil purge.

Ascaridol is given in doses of 15 minims (1 cc.) for adults, on an empty stomach and followed in an hour by a saline purge.

PREPARATION

Chenopodium Oil, *Oleum Chenopodii*, N.F., B.P. *Dosage:* Caution! As an anthelmintic for adults, single dose, 1 cc. (15 minims).

Gentian Violet (Methylrosaniline Chloride)

Gentian violet was introduced as an anthelmintic by Faust (1930). It is the most satisfactory drug for oxyuriasis and strongyloidosis. It is a mixture of pentamethylpararosaniline and hexamethylpararosaniline chlorides. It is soluble in 25 parts of water and in 10 parts of alcohol.

Pharmacological Action.—Besides being an efficient anthelmintic, gentian violet is a useful antiseptic for infected wounds, mucous membranes, and serous surfaces. The drug is valuable in the treatment of burns because of its ability to form a precipitate with necrotic tissues.

Gentian violet acts on the intestinal parasite by producing an intensive blistering effect on the cuticle of the worm. Its efficiency is greatly reduced by the presence of food in the gastrointestinal tract, hence purgation or fasting is indicated before its use.

The drug may be administered as a 1:2,000 solution in a series of daily enemas for three weeks.

Therapeutic Uses.—In the treatment of either oxyuriasis or strongyloidosis Faust recommends a total dosage of 50 grains, to be given

in 1 grain amounts three times daily with meals. In strongyloidosis the drug is prescribed continuously until the total amount has been taken; in oxyuriasis it is administered for eight days, followed by one week of rest, and then repeated for eight days. During both treatment and rest periods the anus should be kept clean. It is well to anoint this region with ointment of ammoniated mercury at regular intervals to prevent reinfection by the eggs.

The *dosage* for children over three years of age is based on 0.01 Gm. a day for each year of apparent (not chronological) age. This daily dosage should be divided into three parts. The treatment is carried out as for adults. Reactions to gentian violet are fairly common, consisting usually of nausea, vomiting, diarrhea, constipation, and slight abdominal pain. If reactions ensue, it is advisable to reduce the dosage or withhold treatment for a day or two until the patient returns to normal. In controlling pinworm infestation within the household, it is necessary to treat all infested members simultaneously in order to reduce opportunity of reinfestation through eggs scattered around the house by nontreated individuals.

Gentian violet is *contraindicated* in moderate to severe heart, hepatic, and renal disease, in gastroenteritis, in pregnancy and in the presence of febrile or debilitating diseases. The patient should abstain from alcohol during the treatment. Persons suffering from ascariasis should be treated for ascarides before the administration of gentian violet.

PREPARATION

Methylrosaniline Chloride, *Methylrosanilinae Chloridum*, U.S.P. (Gentian Violet, Methyl Violet, Crystal Violet). *Dosage:* 60 mg. (1 grain).

Santonin

Santonin ($C_{15}H_{18}O_3$), a glucoside of santonica (Levant wormseed), is one of the oldest of the anthelmintics, having been used against roundworms since the time of Dioscorides. It occurs as a colorless powder or as crystals. It is odorless and possesses a bitter taste. The drug is almost insoluble in water, but soluble in alcohol (1:43). It is frequently used, as it is tasteless and nonirritant, and easily administered to children.

Pharmacological Action.—The drug is readily *absorbed* from the small intestine. Under certain conditions, such as excess bile or alkalinity in the intestine, santonin may cause toxic symptoms. It is changed in the intestine to sodium santoninate; the major portion is *excreted* with the feces. The portion absorbed is changed in the organism by oxidation and passes out in the urine.

The drug apparently is irritant to the worms, causing their passage to the large intestine, from which they are expelled by a purgative. Excessive doses first stimulate and then paralyze the central nervous system, particularly the special sense centers.

Toxicology.—Poisoning from santonin may occur with convulsions or milder symptoms of nausea and vomiting. The gastrointestinal symptoms usually appear first. They are nausea, vomiting, cramps, and diarrhea. Nervous symptoms appear later, such as headache, vertigo, weakness, and unconsciousness. At times there is a profuse diarrhea or dysentery, the heartbeat may become slow and feeble, the blood pressure may fall, and there may be albuminuria and hematuria with painful micturition. In some persons, therapeutic doses affect the retina, resulting in "yellow vision." Objects first appear bluish, then yellow.

This condition usually lasts only a few hours. In some cases the senses of taste and smell and occasionally hearing are deranged.

Treat poisoning by stomach lavage and saline cathartics. Stimulants are indicated for collapse, and ether for convulsions.

Therapeutic Uses.—Santonin is used almost exclusively, and is possibly the most effective remedy, for *Ascaris lumbricoides* (roundworms). It is sometimes used also for the removal of pinworms. It is prescribed either with some inert substance or with a purgative, particularly calomel. In adults the crystals may be prescribed in capsules. For children small crystals may be used with sugar. The following prescription is recommended.

In treatment of roundworms (child of 8 years):

℞

Santonin (cryst.)	0.06 Gm. (gr.j)
Mild Mercurous Chloride	0.03 Gm. (gr.ss)
Lactose	2.00 Gm. (ʒss)

Mix and place in four capsules.

Sig.: One every hour.

Routine.—On the day before treatment begins, give a soft diet followed by a dose of castor oil (two to three ounces) at night. Administer the drug early in the morning before breakfast. One hour later give 1 grain of calomel. Two hours later administer a dose of magnesium sulfate. Repeat treatment in one week if parasites persist in stools.

Ransom (Nelson Loose-Leaf Med.) states: "It may be given in a dose of 1 to 3 grains (0.065 to 0.2 Gm.) to adults, mixed with an equal quantity of calomel, or to children at the rate of ⅙ grain (0.01 Gm.) per year of age, also with calomel. This dose is given two or three days in succession and the treatment repeated in about ten days if eggs are still present in the feces."

PREPARATION

Santonin, *Santoninum*, N.F., B.P. *Dosage:* 0.06 Gm. (1 grain).

Tartar Emetic

Tartar emetic, or antimony and potassium tartrate (see also under Antimony), has been widely and effectively used in the treatment of schistosomiasis.

Dosage: Administer by vein a 6 per cent solution on alternate days. The dose is 0.5 cc. for the first injection, 1 cc. for the second, 1.5 cc. for the third, and 2 cc. thereafter until 24 cc. have been given.

The injection of more dilute solutions lessens the toxic symptoms, such as coughing and muscular stiffness, which usually accompany its administration. *Dosage:* Give an initial dose of 8 cc. of 0.5 per cent solution, increasing by 4 cc. for each subsequent injection given on alternate days until a daily dose of 28 cc. is reached. Continue dose until a total of 444 cc. has been given.

Since the drug is heat labile, it should be added to sterile water or to a 5 per cent dextrose solution which has just been boiled.

Newer Antimony Compounds

Stibophen (Fuadin), N.F., is a less toxic antimony compound which is simpler to administer than tartar emetic but is less effective. It is sodium antimony III bis-catechol-2,4 disulfonate, con-

taining 13.6 per cent of trivalent antimony. It is useful against flukes, and is also used against granuloma inguinale and kala-azar.

Administration: Give intramuscularly 1.5 cc. (7 per cent solution) on the first day, 3.5 cc. on the second, 5 cc. on the third, and 5 cc. every other day until a total of 40 cc. have been given. Repeat in one week if ova are still present in stool after treatment.

Anthiomaline.—Mills (1946) reported this antimony compound to be effective in the treatment of blood flukes. No serious toxic symptoms were associated with its use.

Neostibosan (Ethylstibamine) is a pentavalent antimony-organic mixture (see under Antimony). It is presumed that antimony compounds such as neostibosan are able to kill the adult filarial worms.

In the treatment of *Filaria bancrofti,* neostibosan may be given intramuscularly in doses of 3.3 Gm. on alternate days, for five to seven weeks. (See N.N.R.)

Miscellaneous Anthelmintics

Leche de higuerón or "Higueronia." The fresh latex of *Ficus laurifolia* or *glabrata* is reported to be effective in *whipworm* infestation. Being a proteolytic enzyme it digests the worms.

Acranil.—This compound is an acridine derivative closely related to quinacrine. Berberian (1946) found it effective in the treatment of tapeworms. Children were given 1½ to 7½ grains (0.1 to 0.5 Gm.) according to age. The drug was given on an empty stomach and three hours later a saline purge was given. Treatment was continued in smaller doses for a period of three more days without any further purgation.

Pelletierine tannate is a mixture of the tannates of several alkaloids obtained from pomegranate. Its use in the treatment of tapeworm is mentioned in early writings. This drug is little used today because of the frequency with which it produces toxic symptoms such as cramps, dizziness, and visual disturbances. Blindness has been reported from the use of this drug.

Phenothiazine, widely used as a veterinary vermifuge, has also been used in treating pinworm infestations. The dose recommended is 1 to 2 Gm. daily for seven days (children 0.25 to 0.5 Gm.) with repetition of the course after one week's rest. Administer drug in capsules. Follow treatment closely by red blood count as phenothiazine may produce a severe secondary anemia.

AMEBICIDES

Of the numerous protozoan infections of the human bowel, only two are sufficiently important to warrant discussion here. These are *amebiasis,* caused by *Endamoeba histolytica,* and *giardiasis* produced by *Giardia lamblia.*

Amebiasis is caused by the invasion of the tissues of man by a pathogenic ameba, *Endamoeba histolytica.* Symptoms vary from slight digestive upsets to severe dysentery and constitutional manifestations. In its mildest form, amebiasis consists of the presence of ameba in the lumen of the large intestine with or without some penetration or ulceration of the mucosa. The ameboid form may later migrate to the liver, lungs, brain, and other viscera. About 10 to 20 per cent of the population of the United States is believed to harbor the parasite and act as symptom-free carriers of the parasite.

In severe bowel involvement more severe symptoms occur, such as chronic diarrhea, symptoms of dysentery, and the so-called amebic

colitis. If untreated, amebic hepatis may result and even secondary invasion of the liver causing severe amebic abscesses. Occasionally, lung invasion may occur.

The vegetative form of the parasite, which is responsible for the pathogenicity of the disease, does not survive long outside of the body and is destroyed by gastric acidity. The encysted form is quite resistant and is responsible for transmission of the disease. The cystic form enters the host by way of the mouth.

Three types of compounds are used at present as the main therapeutic agents in the treatment of amebiasis. These *amebicidal drugs* may be classified as follows.

1. The Emetine Group
   - Ipecac
   - Emetine
   - Emetine Bismuth Iodide
2. The Iodoquinoline Derivatives
   - Chiniofon (Yatren)
   - Iodochlorhydroxyquinoline (Vioform)
   - Diiodo-oxyquinoline (Diodoquin)
3. The Arsenicals
   - Carbarsone
   - Acetarsone
4. Miscellaneous Agents
   - Penicillin
   - Sulfasuxidine

THERAPY OF AMEBIASIS

None of the above drugs is effective against all the stages of the disease; therefore, treatment consists of the alternate use of two or more preparations. The most recent trends in the treatment of amebiasis are incorporated in the Army Medical Department plan used near the close of World War II. The following is a résumé of the plan:

Course I (Acute cases with ameba in stools). Emetine hydrochloride daily by hypodermic injection for four to six days, followed immediately by oral administration of emetine-bismuth-iodide for twelve consecutive days. A daily retention enema of chiniofon (yatren) is given with the emetine-bismuth-iodine. Following this treatment, the patient is given diodoquin for twelve successive days. (Carbarsone or acetarsone, by mouth, is a second choice.) The patient may be allowed to get up at this stage. If bacillary dysentery is also present, sulfasuxidine may be administered along with the emetine injections.

Course II (Patients passing cysts but no vegetative forms and free of symptoms). Treat exactly as in Course I but omit emetine injections.

Course III (For patients that resist ordinary treatment). A preliminary course of penicillin and sulfasuxidine may eliminate pyogenic organisms. The patient may now respond satisfactorily to Course I.

If cure is not obtained by the above treatments, allow a rest period of ten days and repeat the entire course. Microscopic examinations of the stools for at least six consecutive days, two weeks after treatment, will establish the success or failure of the treatment.

Ipecac

Ipecac was introduced into Europe in 1658 from Brazil where natives used the root in the treatment of diarrheas. The action of ipecac depends on its active principles, the alkaloids, emetine, and cephaeline. Emetine constitutes more than one-half of the total alkaloid content of ipecac. It is a more active amebicide than cephaeline and is more toxic to the heart, while the latter causes more nausea and vomiting.

Action and Uses.—Besides possessing amebicidal action, ipecac possesses expectorant and emetic action. It possesses all of the actions of emetine as well as the added effect of cephaeline. The drug is usually employed in amebiasis when the patient has proved refractory to other treatment. It is usually prescribed in salol-coated pills as a means of lessening the severe gastric irritation and vomiting. The course of treatment for amebiasis may be as follows: Administer 10 to 15 pills (0.3 Gm. each) at night before retiring. The full course consists of 100 pills and the patient should have absolute bed rest during treatment.

Emetine

The principal constituents of ipecac are *emetine* (1-2 per cent), cephaeline, tannic acid, etc. Emetine, which is methyl cephaeline, constitutes about 63 per cent of the total alkaloids. It is more antiamebic and considerably less emetic than cephaeline. The action of ipecac is due entirely to its alkaloids emetine and cephaeline; emetine is to be preferred in medicine. Emetine was used successfully in medicine by Rogers (1913). It has important advantages over powdered ipecac, in accuracy, effectiveness, and ease of administration.

Pharmacological Action.—Emetine is a strong irritant of all mucous membranes, such as the eye, nose, etc. When taken orally it produces irritation of the stomach and intestine, causing vomiting and diarrhea.

Hypodermic injections of emetine hydrochloride produce gastrointestinal irritation and vomiting, but the hypodermic emetic dose (approx. 0.06 Gm.) is ten times the oral emetic dose. The emetic action is longer when the drug is given hypodermically, therefore the drug probably has no central action. The drug is eliminated slowly, hence the action is cumulative, and continued administration of moderate doses may result in poisoning.

Toxicology.—Emetine causes vomiting by its action on the mucous membrane of the stomach. If given in large doses it causes intestinal irritation, cardiac weakness, fall in blood pressure, and even cardiac paralysis. Clinical accidents have occurred from doses of 25 mg. per Kg. (Leibly, 1930). These accidents may be explained by its cumulative action. Effective treatment is accompanied by toxic phenomena in a high percentage of the cases treated (80%) (Dobell and Bishop, 1929). It is contraindicated in patients with symptoms of heart failure or metabolic diseases.

Therapeutic Uses.—Emetine hydrochloride is emetic and amebicidal. It is seldom used as an emetic, or for routine treatment of amebiasis, but is valuable in association with other amebicides.

Dosage: Administer emetine hydrochloride by muscular injection 30 mg. (½ grain) twice daily for four to six days. Extend treatment to twelve days only in cases of recalcitrant hepatic amebiasis. Intravenous administration is dangerous and subcutaneous injections are often painful and discolor the skin.

PREPARATION

Emetine Hydrochloride, *Emetinae Hydrochloridum*, U.S.P., B.P. *Dosage:* 0.06 Gm. (1 grain).

Emetine-Bismuth-Iodide

Numerous insoluble emetine preparations have been prepared for oral use in the treatment of amebiasis. These preparations are less reliable than the parenteral preparations and may cause more gastrointestinal disturbances.

Emetine-bismuth-iodide is probably the most useful of the oral preparations. The iodine content of this preparation may contribute to some of its effectiveness. This agent is given by mouth in doses of 0.2 Gm. (3 grains) daily for twelve consecutive days. Administer in a gelatin capsule on retiring at night. A barbiturate may be given to allay nausea.

Chiniofon (Yatren)

Chiniofon is a mixture of 7-iodo-8-hydroxyquinoline-5-sulfonic acid, sodium bicarbonate and sodium iodohydroxyquinolinesulfonate, containing from 26.5 to 28.9 per cent iodine.

Chiniofon powder is employed principally in the treatment of intestinal amebiasis. It is claimed that this drug acts locally upon amebae in the alimentary tract and also through the blood stream upon those embedded in the mucosa. Toxic symptoms are rare, but diarrhea may result from its oral use.

Consecutive series of chiniofon enemas are given daily for twelve days. The strength usually employed to start with is 200 cc. of 2.5 per cent and then increasing the strength if it is well tolerated. Oral administration is rarely employed because of diarrhea and the scalding sensation during defacation.

PREPARATIONS

Chiniofon, *Chiniofonum*, U.S.P. Iodine about 27%. *Dosage:* 1 Gm. (15 grains).

Chiniofon Tablets, *Tabellae Chiniofoni*, U.S.P. *Dosage:* The usual size contains 0.25 Gm.

Iodochlorohydroxyquinoline (Vioform)

Iodochlorhydroxyquinoline, Vioform (N.N.R.), $C_9H_4N.OH.I.Cl$, is a grayish powder almost insoluble in water and sparingly soluble in alcohol.

This drug is used against *trichomoniasis*, *vaginitis*, and internally, against *amebiasis*. Like chiniofon, it is effective only in intestinal amebiasis, especially the chronic type, and acts both on the motile and cystic forms of amebas. Vioform is also used locally as a dusting powder on wounds, ulcers, burns, and exudative skin eruptions. Against amebiasis, 0.75 gram to 1.0 gram daily is administered in capsules in divided doses of 0.25 gram by mouth for ten days. The course may be repeated after a rest period of ten days. Toxic symptoms, such as gastrointestinal irritation, have been reported. Vioform should be used with caution in patients with liver damage. Iodism should be kept in mind and also the possible effect on a patient with goiter.

Diiodo-oxyquinoline (Diodoquin)

Diodoquin is a more recent drug of this group. It is apparently poorly absorbed and relatively nontoxic. However, attacks of abdominal pain, diarrhea, and headache have been reported.

The dose is 3 tablets, each 0.2 Gm. (3 grains), three times daily for 20 days. Results have been consistently good.

Carbarsone

Carbarsone, p-carbamido-phenylarsonic acid, $NH_2.CONH.C_6H_4.As{:}O{:}(OH)_2$ is a complex arsenic compound containing about 28 per cent arsenic. It is a white powder, slightly soluble in water and in alcohol, and freely soluble in alkalies.

Pharmacological Action.—Carbarsone is directly amebicidal by virtue of its arsenic content. It is readily absorbed after oral administration and is excreted slowly in the urine. Rest periods between courses are indicated because of its tendency to cumulate in the body. Like chiniofon, the action of carbarsone on motile forms is not as effective as that of emetine. Carbarsone does not act on amebas in abscesses of the liver and other organs.

Toxicology.—Few cases of poisoning have been reported relative to the therapy with carbarsone. Skin rashes and localized edemas have been reported. Severe exfoliative dermatitis is practically unknown. Death following its use is very rare.

Therapeutic Uses.—Reed (1935) places carbarsone in first place among the amebicidal drugs. It has the advantage that it can be given both orally and rectally. Recently, however, the iodoquinoline derivatives have been a favorite of the more experienced clinicians.

Dosage: Carbarsone is given in 0.25 Gm. (4 grains) capsules twice daily after meals for twelve days. Rectal administration is also satisfactory. When giving carbarsone rectally, first give a cleansing soda enema, followed in one hour by instillation in the rectum of 200 cc. of 1 per cent sodium bicarbonate. Precede enema by the oral administration of 0.2 Gm. (3 grains) of sodium amytal to insure sleep and aid retention of enema. Repeat enemas on alternate nights until five have been given. This course may replace the oral administration but should not be administered at the same time.

The drug is contraindicated in patients exhibiting gastrointestinal upset, respiratory distress, visual disturbances, jaundice, certain skin manifestations, and any evidences of renal damage or liver and spleen enlargement.

Acetarsone (Stovarsol) was introduced as an amebicide in 1923. It is seldom used because of its toxicity.

Preparation

Carbarsone, *Carbarsonum*, U.S.P. *Dosage:* 0.2 Gm. (3 grains).

Miscellaneous Agents

Penicillin has been tried with excellent results (Hargreaves, 1945) in patients not responding to the ordinary treatment of amebic infection. It is reported to bring about dramatic symptomatic relief.

Sulfasuxidine has been tried to combat some of the organisms not responsive to penicillin. Its use has been successful in rendering refractory patients more amenable to ordinary treatment.

That one drug alone probably will not suffice in the treatment of amebiasis has been shown by many and quite recently re-emphasized by Hayward, 1946. The following course was followed among the British

Middle East Forces: Emetine, 1 grain (60 mg.) daily with quinoxyl (2.5 per cent) enema for 10 days. Carbarsone, 0.25 Gm. two times a day for eight days followed by emetine bismuth iodide, 3 grains (0.2 Gm.) for twelve days.

References

Sulfonamides

Beyer, K. H., Russo, H. F., Patch, E. A., Peters, L., and Sprague, K. L.: The Formation and Excretion of Acetylated Sulfonamides, J. Lab. & Clin. Med. 31: 65, 1946.

Bigler, J. A., and Haralambi, J. Q.: Sulfanilamide and Related Compounds; Review of Literature, Am. J. Dis. Child. 57: 1110, May, 1939.

Collins, E. N., and Hewlett, J. S.: Succinylsulfathiazole (Sulfasuxidine) in Treatment of Chronic Ulcerative Colitis: Report of 55 Cases Followed Two Years; Its Value by Retention Enema in Early Cases, Gastroenterology 7: 549, 1946.

Council Report: Dangers From the External Use of Sulfonamides, J. A. M. A. 128: 1024, 1945.

Dowling, H. F., Hirsch, H. L., and Lepper, M. H.: Toxic Reactions Accompanying Second Course of Sulfonamides in Patients Developing Toxic Reactions During a Previous Course, Ann. Int. Med. 25: 950, 1946.

Gilligan, D. R.: Comparative Studies of the Chemical Changes Occurring in Sulfonamide Drugs During Therapy in Man, J. Clin. Investigation 24: 301, 1945.

Grand, M. J. H., Stanbury, J. B., Ekermeyer, E. W., and Purvis, J. D., Jr.: Rheumatic Fever: Statistical Analysis of Incidence During Sulfadiazine Prophylaxis, U. S. Nav. M. Bull. 46: 1793, 1946.

Guides to Therapy for Medical Officers, Washington, 1942, United States Government Printing Office.

Keefer, C. S.: Toxic Reactions Following Sulfonamide Treatment, New England J. Med. 226: 266, Feb., 1942.

Lees, R.: Treatment of Sulphonamide-Resistant Gonorrhoea With Penicillin, Brit. M. J. 1: 605, 1946.

Long, P. H., and Bliss, E. A.: The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, 1939, The Macmillan Co.

New and Nonofficial Remedies, Chicago, 1948, American Medical Association.

Northey, E. N.: The Sulphonamides and Allied Compounds, New York, 1948, Reinhold Publishing Corp.

O'Donnell, C. H., Posch, J. L., and Hirshfeld, J. W.: A Study of the Values of Local Sulfathiazole in Operative Wounds in the Prophylaxis of Infection, Surg., Gynec. & Obst. 82: 323, 1946.

Oldham, F. K., Kelsey, F. E., and Geiling, E. M. K.: Essentials of Pharmacology, Philadelphia, 1947, J. B. Lippincott Co.

Woolley, D. W.: Recent Advances in the Study of Biological Competition Between Structurally Related Compounds, Physiol. Rev. 27: 308, 1947.

Penicillin

Chain, E., Florey, H. W., Gardner, A. D., Heatley, N. G., Jennings, M. A., Orr-Ewing, J., and Sanders, A. G.: Penicillin as a Chemotherapeutic Agent, Lancet 2: 226-228 (Aug. 24), 1940.

Eagle, H.: The Therapeutic Activity of Penicillin F, G. K and X in Experimental Infections With Pneumococcus Type I and *Streptococcus pyogenes*, J. Exper. Med. **85**: 175, 1947.

Fleming, Sir Alexander: Penicillin, Its Practical Application, Philadelphia, 1946, Blakiston Co.

Heller, Jr., J. R.: Results of Rapid Treatment of Early Syphilis, J. A. M. A. **132**: 258, 1946.

Herrell, W. L.: Penicillin and Other Antibiotic Agents, ed. 2, Philadelphia, 1947, W. B. Saunders Co.

Keefer, C. S., et al.: Penicillin in the Treatment of Infections (A Report of 500 Cases), J. A. M. A. **122**: 1217, 1943.

Kolmer, John A.: Penicillin Therapy, Including Tyrothricin and Other Antibiotic Therapy, New York, 1947, D. Appleton-Century Co.

Krasno, L., Karp, M., and Rhoads, P. S.: Inhalation of Penicillin Dust, J. A. M. A. **138**: 344, 1948.

Meleney, F. L.: Penicillin in the Treatment of Established Surgical Infections—A Systemic Study of 744 Including 82 Septicemias, Ann. Surg. **124**: 962, 1946.

Rake, Geoffrey, and Richardson, A. P.: Pharmacology of Penicillin, Ann. New York Acad. Sc. **48**: 143, 1946.

du Vigneaud, V., Carpenter, F. H., Holley, R. W., Livermore, A. H., and Rochele, J. R.: Synthetic Penicillin, Science **104**: 431, 1946.

Walker, A. E., and Johnson, H. C.: The Clinical Study of Penicillin, Science **105**: 653, 1947.

Walker, A. E., and Johnson, H. C.: The Changing Character of Commercial Penicillin—With Suggestions as to the Use of Penicillin in Syphilis, J. A. M. A. **131**: 271, 1946.

Streptomycin

Adcock, J. D., and Hettig, R. A.: Absorption, Distribution and Excretion of Streptomycin, Arch. Int. Med. **77**: 179, 1946.

Deyke, V. F., and Wallace, J. B.: Development of Aplastic Anemia During the Use of Streptomycin, J. A. M. A. **136**: 1098, April 24, 1948.

Dubos, R. J.: Bacteriostatic and Bactericidal Agents Obtained From Saprophytic Microorganisms, J. Pediat. **19**: 588, 1941.

Farrington, R. F., Hull-Smith, H., Bunn, P. A., and McDermott, W.: Streptomycin Toxicity, Reactions to Highly Purified Drug on Long-Continued Administration to Human Subjects, J. A. M. A. **134**: 679, 1947.

Hinshaw, H. C., Feldman, W. H., and Pfuetze, K. H.: Treatment of Tuberculosis With Streptomycin—A Summary of Observations on One Hundred Cases, J. A. M. A. **132**: 778, 1946.

Levine, E. R., Klein, W. S., and Froman, A.: Streptomycin as Adjunct in Treatment of Acute Pulmonary Tuberculosis, J. A. M. A. **138**: 808, 1948.

Pulaski, E. J.: Streptomycin in Surgical Infections: II. Infections of the Genito-urinary Tract, Ann. Surg. **124**: 392, 1946.

Waksman, S. A., and Schatz, A.: Streptomycin—Origin, Nature, and Properties, J. Am. Pharm. A. **34**: 273, 1945.

Tyrothricin

Gause, G. F., and Brazhnikova, M. G.: Gramicidin S, Origin and Mode of Action, Lancet **2**: 715, 1944.

Henderson, J.: The Status of Tyrothricin as an Antibiotic Agent for Topical Application, J. Am. Pharm. A., Sc. Ed. **35**: 141, 1946.

Polymyxin

Schoenbach, E. B., Bryer, M. S., Bliss, E. A., and Long, P. H.: Polymyxin—A Note on Experimental and Clinical Investigations, J. A. M. A. **136**: 1096, April 24, 1948.

Aureomycin

Braley, A. E., and Sanders, M.: Aureomycin in Ocular Infections, J. A. M. A. **138**: 426, 1948.

Finland, M., Collins, H. S., and Paine, T. F., Jr.: Aureomycin, a New Antibiotic, J. A. M. A. **138**: 946, 1948.

Schoenbach, E. B., and Bryer, M. S.: Treatment of Atypical Pneumonia With Aureomycin, J. A. M. A. **139**: 275, 1949.

Wright, L. T., Sanders, M., Logan, M. A., Prigot, A., and Hill, L. M.: Aureomycin: A New Antibiotic With Virucidal Properties, J. A. M. A. **138**: 408, 1948.

Bacitracin

Anderson, H. H., Villela, G. G., Hansen, E. L., and Reed, R. K.: Some Physical and Biologic Properties of Subtilin and Other Antibiotics, Science **103**: 419, 1946.

Johnson, B. A., Anker, H., and Meleney, F. L.: Bacitracin: a New Antibiotic Produced by a Member of the *B. subtilis* Group, Science **102**: 376, 1945.

Meleney, F. L., and Johnson, B.: Bacitracin Therapy—the First Hundred Cases of Surgical Infections Treated Locally With the Antibiotic, J. A. M. A. **133**: 675, 1947.

Anthelmintics

Top, F. H.: Communicable Diseases, ed. 2, St. Louis, 1947, The C. V. Mosby Co.

Faust, E. C.: Use of Anthelmintics, J. A. M. A. **108**: 386, 1937. Chemotherapy of Intestinal Parasites, J. A. M. A. **117**: 1331, 1941.

Lamson, P. D.: Ten Years' Experience With Anthelmintics, Baltimore, 1936, Waverly Press.

Amebicides

Chopra, R. N.: A Handbook of Tropical Therapeutics, Calcutta, 1936, Art Press.

Hayward, G. W.: Amebiasis in Italy, Brit. M. J. **2**: 457, 1946.

Leake, C. D.: Chemotherapy of Amebiasis, J. A. M. A. **98**: 195-199, 1932.

Reed, A. C.: Treatment of Amebiasis, J. A. M. A. **103**: 1224, 1934.

Rogers: Recent Advances in Tropical Medicine, London, 1929, Churchill, Chapters XI and XII.

Tallant, E. J., Maisel, A. L., and Rakestraw, M. R.: Amebiasis Among American Armed Forces, Arch. Int. Med. **77**: 597, 1946.

CHAPTER IX

ANTISEPTICS, DISINFECTANTS, AND ANTI-INFECTIVES

III. ANTI-INFECTIVES (Continued)

ANTISYPHILITIC DRUGS

The drugs used in the treatment of syphilis will be discussed first, and then their practical application will be presented. During the last four or five years two innovations in the therapy of syphilis are apparent—first, the shortening of the periods of treatment, and, second, the introduction of penicillin, an active and relatively nontoxic spirocheticide. The organic arsenicals, bismuth preparations, mercury preparations, iodides, and penicillin will be discussed in their relation to the therapy of syphilis.

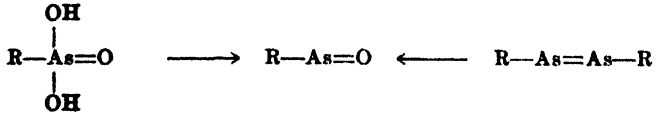
Organic Arsenic Compounds

Various organic arsenic compounds have been introduced into medicine to improve the therapeutic action of inorganic forms. The organic or nonionic forms do not immediately produce typical arsenic effects but slowly free more or less active ionic arsenic which produces typical arsenic reactions. This reduction or modification in the body occurs at widely different rates for the different compounds which may account for some of the differences in their actions.

The organic compounds, or some of their derivatives, differ from the inorganic forms in the following important details:

1. The organic compounds are less toxic to mammals and more toxic to protozoan parasites.
2. Some remain in the blood for a longer period than does the inorganic arsenic compound, and thus remains longer in contact with parasites which are to be killed.
3. The organic compounds are more toxic to the parasites than to the host.
4. The organic arsenic compounds are thought to be changed to more active forms in the body.

Mode of Action of Organic Arsenicals.—Typical arsenic action results from trivalent arsenic. *The arsenic in pentavalent compounds must be reduced to the trivalent form before a typical arsenic reaction results.* Some workers believe that the arsphenamines pass through the "arsenoxide" stage before they produce their beneficial actions. The reactions may be as follows:



Pentavalent type — Arsenoxide — Trivalent type

The reduction to the trivalent form occurs in the body and varies greatly with the different compounds. In some cases the effects produced by these compounds are due to arsenic which is slowly rendered active;

in others, the therapeutic effects may be due in part at least to unaltered molecules. Since in the body the organic compounds are less toxic to mammals and more toxic to protozoan parasites, they become available for combating trypanosomiasis, treponematosis, and other protozoan infections.

The action of arsenoxides is believed to be due to their reaction on the sulfhydryl compounds in the cells in which they are absorbed. This view is supported by the chemical reaction between arsenoxides and compounds possessing free sulfhydryl groups and by the antidotal action of such compounds as cysteine, glutathione, and BAL, which are sulfhydryl compounds, against toxic doses of arsenoxides and arsphenamines.

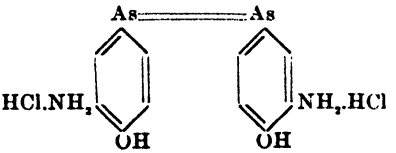
Classification of Common Organic Arsenicals

The discovery of salvarsan was a great step forward in the treatment of syphilis, but its use is attended by certain difficulties. This fact has stimulated research and resulted in the preparation of many new organic arsenicals. None has any marked superiority over salvarsan and neosalvarsan but several possess certain characteristics which make them valuable in the field of therapeutics.

Organic arsenic compounds may be divided into trivalent and pentavalent forms. The following are described:

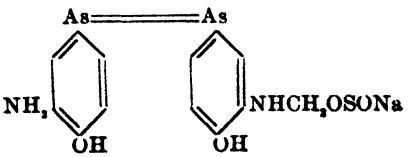
I. Trivalent Arsenic Compounds

A. Arsphenamine (Salvarsan)



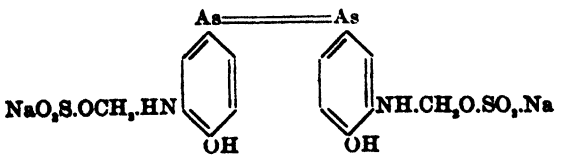
(3-Di-hydroxy-4-diamino-arseno-benzene hydrochloride)

B. Neoarsphenamine (Neosalvarsan)



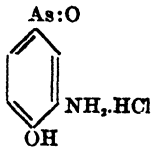
(Sodium 3,3'-diamino-4,4'-dihydroxyarsenobenzene methanol sulfoxylate)

C. Sulfarsphenamine (Sulfarsenol)



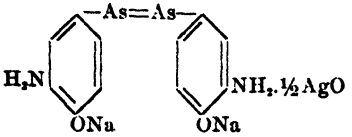
(Arsphenamine-dimethylene sulfonate)

D. Mapharsen



(3-amino-4-hydroxy phenylarsine oxide hydrochloride)

E. Silver Arsphenamine

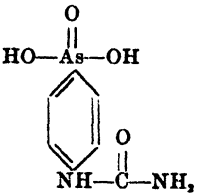


F. Bismuth Sulfarsphenamine (Bismarsen)

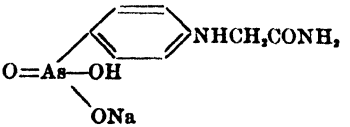
The sodium salt of a bismuth derivative of arsphenamine methylene sulfonic acid (the exact formula not established).

II. Pentavalent Arsenic Compounds

G. Carbarsone

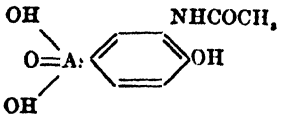


H. Tryparsamide



(Sodium n-phenyl glucinamide p-arsenate)

I. Acetarsone



(Acetyl-amino-hydroxyphenyl-arsonic acid)

Toxicology of Organic Arsenicals

In administering organic arsenicals by vein, great care should be exercised that no drug escapes in the subcutaneous tissues, for it produces a severe cellulitis. Toxic action may be due to error in the manufacture, to errors in technic of administration, and to an idio-

syncrasy on the part of the patient. The deleterious action of neoarsphenamine may be due to its altering the colloidal equilibrium of the blood. Turbid samples should be discarded. The reaction of patients to organic arsenicals is extremely variable.

General reactions to arsphenamine include nitritoid reaction, the Jarisch-Herxheimer reaction, skin reactions, blood dyscrasias, central nervous system disturbances, gastrointestinal upsets, and renal injuries.

Among the mild manifestations are the *"nitritoid reaction,"* a state resembling shock and possibly due to multiple pulmonary embolism. It is characterized by flushing of the face, edema of the tongue and lips, nausea and vomiting, profuse perspiration, fall in blood pressure, and a feeling of anxiety. It resembles the effects produced by the administration of nitrites, thus the name "nitritoid" reaction or crisis.

Severe types of reactions include dermatitis, hepatitis, blood changes, and hemorrhagic encephalitis. The drugs can produce about any form of dermatitis, due in part to overdosage and also to sensitization. The most severe reaction is exfoliative dermatitis. Another reaction is an erythema which occurs within the first two weeks after the first injection.

Another toxic manifestation, the Jarisch-Herxheimer reaction, may appear from two to three hours after injection. It is due to sudden liberation of syphilitic toxins locally in the lesions. It is characterized by an exacerbation of the nitritoid reactions or intensification of early reactions. This reaction may be avoided by preliminary treatment with small doses of arsphenamine or by preparation treatment with bismuth or mercury preparations and potassium iodide. Agranulocytosis, peripheral neuritis, purpura hemorrhagica, and encephalomyelitis are rare, but serious complications follow arsenical therapy. Gastrointestinal upsets are frequent. Jaundice may occur during the course of treatment.

Treatment.—When the *"nitritoid reaction"* occurs, stop injection of drug and administer 0.5 cc. of epinephrine solution hypodermically. The reaction is usually not as serious as it appears to be. Treatment can usually be continued by use of other arsenical drugs and a change of procedure. *Gastrointestinal symptoms* may be kept at a minimum by avoiding food for three hours before and after treatment. The *Herxheimer reaction* is usually not serious in early syphilis. The treatment is given in the preceding paragraph.

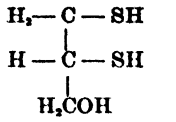
Dermatitis, especially dermatitis exfoliativa, is a serious complication. Any signs or symptoms which precede this reaction, such as pruritus, little patches of dermatitis on the arms or neck, indicate that treatment should be discontinued. Sodium thiosulfate in 0.5 to 1.0 Gm. doses given daily for four or five days, together with soothing applications, colloid baths, forced fluids, and alkalies, is of benefit. "BAL" is the treatment of choice in organic arsenical poisoning.

Jaundice may be due to the toxic effects of an arsenical drug on the liver. Treatment with arsenicals must be stopped. Administer glucose intravenously to protect the liver. *Purpura* and *hemorrhage* are warning signals of thrombocytopenia, granulocytopenia or aplastic anemia. These reactions are often fatal but are fortunately rare. If they do occur, stop drug and give transfusions.

BAL (Dimercaprol)

BAL (British Anti-Lewsite, 2,3-dimercaptopropanol) was introduced by British scientists, Peters, Stockey, and Thompson during World

War II. They developed the substance on the basis of a fundamental theoretic concept, which lead to in vitro studies, indicating that it was able to compete successfully with thiol-containing tissue enzymes, in attracting the poisonous metallic ion.



2,-3-dimercaptopropanol (BAL)

Dosage: BAL dose (10 per cent solution in peanut oil and benzyl benzoate): 0.25 cc. per 10 kilograms body weight (4 minims per 22 pounds) intramuscularly, repeated four times at four-hour intervals during the first two days, then twice on third day, and once daily for the next five days. *Severe Poisoning:* Increase dose to 0.3 cc. per 10 kolgrams every four hours for two days, then four injections on third day, two on the fourth and one thereafter for ten days.

Overdosage with BAL leads to acidosis and hyperglycemia, increased rate of respiration, tremors, convulsions, and tachycardia. Other symptoms include nausea, vomiting, headache, burning sensation in mouth, throat and eyes, muscular aches, and elevated blood pressure. The side effects are usually maximum at fifteen to twenty minutes after intramuscular injection. Barbiturates have been recommended as an antidote for the more severe side effects of BAL.

ORGANIC ARSENICALS

The organic arsenicals comprise an important group of chemotherapeutic drugs. Those especially useful in syphilis include the arsphenamines, oxophenarsine, dichlorophenarsine and tryparsamide.

Arsphenamine (Salvarsan)

Arsphenamine or diaminodihydroxyarsenobenzene contains 31 per cent arsenic. It is a yellow, odorless, hygroscopic powder, soluble in water, alcohol, and glycerin. In the dry state or in solution it is oxidized on exposure to air, becoming darker and more toxic.

Arsphenamine is useful as a specific remedy for syphilis in all stages but is more efficient in early infections. It is especially useful in the primary stage; in the later stages continuous medication should be maintained for some time by alternating courses of arsenic and bismuth preparations. The remedy is contraindicated in severe disturbances of the circulatory organs, advanced degeneration of the central nervous system, and cachexias, unless these are a direct result of syphilis. It has also been employed successfully in various types of syphilitic diseases of the eyes. *Dosage:* Caution! Intravenous 0.3 Gm. (U.S.P.) dissolved in warm water without shaking. ***Prior to injection the solution must be alkalinized with 0.85 cc. of normal sodium hydroxide for each 0.1 Gm. of arsphenamine (U.S.P.).*** Its use by anyone who has not mastered the proper technic is dangerous.

Neoarsphenamine (Neosalvarsan)

Neoarsphenamine contains about 20 per cent arsenic. It must be kept in sealed colorless glass from which air is excluded and in a cool place, preferably not over 25° C. It is a yellow, odorless powder, readily oxidized in the dry state or in solution by exposure to air, becoming darker and more toxic. It is very soluble in water, soluble in glycerin, slightly soluble in alcohol.

Neoarsphenamine is similar to arsphenamine. It is preferred especially in general practice because its administration is much simpler, and less liable to cause fatalities from errors in technic. The solutions, however, oxidize rapidly; therefore, they should be used within twenty minutes. Neoarsphenamine is always injected intravenously. It is somewhat less active than arsphenamine and slightly higher doses and a more prolonged period of treatment are usually indicated. However, neoarsphenamine is sufficiently effective in practice.

Arsphenamine vs. Neoarsphenamine.—Arsphenamine gives an acid solution and must be carefully neutralized before use; otherwise serious accidents will occur. On the other hand, neoarsphenamine forms a neutral solution with water which can be injected immediately. The latter is not hemolytic in ordinary solution, being hemolytic only when very dilute or very concentrated. Arsphenamine hemolyzes with practically all concentrations. It is more stable in air and gives more uniform and prompt results.

Other Arsphenamines

Sulfarsphenamine is about as active as neoarsphenamine. It can be injected intramuscularly, which is of particular value in children. Silver arsphenamine also is about as active as neoarsphenamine, being slightly less toxic. Argyria might occur if treatment is long continued. Solutions must be injected within twenty minutes after preparation, else they deteriorate by oxidation.

Bismarsen (bismuth arsphenamine sulfonate) is a water-soluble preparation containing about 13 per cent arsenic and 24 per cent bismuth. It must be administered by muscle, since its intravenous use is attended by severe toxic reactions. It is slow acting and relatively weak but is of value when intravenous medication is indicated. (The mode of action, toxicity, etc., of the arsphenamines are discussed in details under arsenic.)

Preparations

Arsphenamine, *Arsphenamina,* U.S.P. *Dosage:* See above discussion.

Neoarsphenamine, *Neoarsphenamina,* U.S.P. *Dosage:* Caution! Intravenous 0.45 Gm. (6½ grains), dissolved in cold water.

Sulfarsphenamine, *Sulfarsphenamina,* U.S.P. *Dosage:* Intramuscular, 0.45 Gm. (6½ grains).

Silver Arsphenamine, N.N.R., contains about 19 per cent arsenic and from 12 to 14 per cent silver. *Dosage:* From 0.1 Gm. to 0.3 Gm. (1½ to 5 grains) for adults. For details see N.N.R.

Bismarsen, N.N.R., bismuth arsphenamine sulfonate. *Dosage:* 0.1 to 0.2 Gm. (1½ to 3 grains) intramuscularly weekly. Children: 2 weeks, 15 mg. (¼ grain); 3 months, 50 mg. (¾ grain); 2 years, 100 mg. (1½ grains); 8 years, 200 mg. (3 grains).

Oxophenarsine Hydrochloride (Mapharsen)

Oxophenarsine is the arsenoxide of arsphenamine. It is a pure chemical compound available in crystalline form. It is relatively unstable even in the dry state, becoming brownish in color and more toxic. It is administered intravenously and does not require alkalinization. The reactions following its use are less severe than those of arsphenamines, and the effective dosage is much less than for the latter.

The great effectiveness and rapidity of action have led to the almost exclusive use of oxophenarsine in the intensive arsenotherapy of

syphilis. The procedure consists of continuous intravenous administration or repeated injections at frequent intervals over periods varying from five to twenty days. The shorter periods of treatment are associated by a higher incidence of toxic manifestations. The *one day treatment* so often spoken of consists of intensive chemotherapy and fever therapy over twenty-four hours. The results are usually poor and the incidence of toxic reactions high.

Dichlorophenarsine hydrochloride is also used in the arsenical treatment of syphilis; its uses and effectiveness are somewhat like those of oxophenarsine. It is rapidly broken down in the body to oxophenarsine. Dichlorophenarsine offers the advantage of greater stability in storage. It is mixed with an alkaline buffer for preparation of solutions for injection.

The *trend of clinical practice* is toward the use of oxophenarsine hydrochloride (mapharsen), or the dichlorophenarsine hydrochloride. Therapeutic results are fully as good as with the arsphenamines. Nitritoid reactions are absent and other toxicities are about the same.

Tryparsamide

Tryparsamide is a pentavalent arsenic derivative highly effective in certain forms of trypanosomiasis. Its spirocheticidal action is weak but it is especially useful in syphilis of the central nervous system because of its ability to penetrate tissues more readily than most arsenicals.

Tryparsamide probably does not act as a treponemicide as it is almost ineffective against the primary and secondary stages of syphilis, and against the gummata. Its great value is in disseminated sclerosis, before irreparable degeneration of the nerve cells. The toxic effects resemble those of other pentavalent arsenic compounds. The possibility of visual injury, a specific toxic effect on the optic nerve, requires caution.

Preparations

Oxophenarsine Hydrochloride, *Oxophenarsinae Hydrochloridum*, U.S.P. *Dosage:* Intravenous, 45 mg. (⅔ grain). The initial dose is 30 mg. for women; 40 mg. for men; 0.5 mg. per kilogram of body weight for children. The maximum adult dose is 60 mg., the average, 40 to 50 mg., given once every four or five days. The average dose for children lies between 0.5 to 1.0 mg. per kilogram, given at the same intervals.

Dichlorophenarsine Hydrochloride, *Dichlorophenarsinae Hydrochloridum*, U.S.P. *Dosage:* Intravenous, 45 mg. (⅔ grain). The maximum dose is 68 mg. Injections are given every four to five days. For children, the initial dose should not exceed 0.5 mg. and subsequent doses should lie between 0.5 and 1.0 mg. per kilogram of body weight.

Tryparsamide, *Tryparsamidum*, U.S.P. Arsenic about 25 per cent. *Dosage:* Caution! Intravenous, 2 Gm. (30 grains).

BISMUTH

Bismuth is the preferred heavy metal in the treatment of syphilis. It is less toxic than mercury, particularly for the kidney, and more potent. The promptness and degree of antisyphilitic action of bismuth are between that of arsphenamine and mercury. It may be substituted for either, especially with patients in whom these drugs are contraindicated or have failed to act.

The most commonly used preparation is bismuth subsalicylate. This is given once weekly, intramuscularly, 1 cc. of a 10 per cent suspension in sesame oil. There is á tendency for deposits of this compound to remain in the muscle, often causing local fibrosis. Therefore, water-soluble compounds have been introduced. Of these, Iodobismitol is the drug of choice. It need be injected less often than others—the dose being 2 cc. intramuscularly once or twice a week.

Oral bismuth preparations, equally as effective as those given by muscle, are available. These preparations are for those who cannot tolerate injections. Sobisminol mass may be taken orally—the adult dosage is two capsules (0.15 Gm. bismuth each) taken three times a day between meals with water or milk.

Toxic effects of bismuth are rare. The only commonly observed toxic effect is stomatitis, which seldom occurs if the proper oral hygiene is observed.

PREPARATIONS

Bismuth Subsalicylate, *Bismuthi Subsalicylas*, U.S.P. Specific therapy in syphilis: 0.013 Gm. (2 grains, usually in 1 cc.) in oil intramuscularly, weekly. Children: 2 weeks, 0.2 cc. (3 minims); 3 months, 0.3 cc. (5 minims); 2 years, 0.5 cc. (8 minims); 8 years, 1 cc. (15 minims).

Bismuth Subsalicylate Injection, *Injectio Bismuthi Subsalicylatis*, U.S.P. A sterile suspension of bismuth subsalicylate in a suitable fixed oil. It contains an amount of bismuth equivalent to about 58 per cent of the labeled amount of bismuth subsalicylate, including all tolerances. The usual sizes contain 0.1 Gm. or 0.12 Gm. in 1 cc.

Iodobismuthite Sodium with Ethylaminobenzoate, N.N.R., or Iodobismitol with Benzocaine, N.N.R. Antisyphilitic: 2 cc. (30 minims) intramuscularly once or twice a week.

Sobisminol Mass, N.N.R. A complex organic bismuth product. It contains between 19.25 and 20.25 per cent of bismuth: 0.75 Gm. of sobisminol mass represents 150 mg. of bismuth. *Dosage:* Adult dosage, from two to three capsules three times a day, taken with plenty of water. Each capsule represents 150 mg. of metallic bismuth. (See N.N.R.)

MERCURY

Mercury has been used in the treatment of syphilis for centuries. The action of mercury is slower than either arsphenamine or bismuth and is highly toxic. In the early stage the Treponemas disappear from the lesions, and the symptoms subside. The invasion, however, recurs unless treatment is continued for some time. Mercury may be substituted when bismuth is ineffective, toxic, or otherwise contraindicated. The most desirable preparation is mercuric salicylate, given in a dose of 60 mg. intramuscularly, once or twice a week.

Before the introduction of the bismuth preparations, mercury preparations were used in conjunction with arsenicals. Now, however, they are used topically for prevention of infection, calomel ointment being commonly used for this purpose.

PREPARATIONS

Mild Mercurous Chloride Ointment, *Unguentum Hydrargyri Chloridi Mitis*, N.F. (Calomel Ointment). Mild Mercurous Chloride (30 per cent) with white petrolatum and hydrous wool fat. Used by inunction for venereal prophylaxis.

Mercuric Salicylate Ampuls, *Ampullae Hydrargyri Salicylatis,* N.F. (Mercuric Salicylate Injection). Contains an amount of mercury equivalent to 56 per cent of the labeled amount of mercuric salicylate in a suitable fixed oil. The usual size contains 0.06 Gm., 0.1 Gm., and 0.12 Gm. mercuric salicylate in 1 cc. of oil. *Dosage:* Intramuscular 0.1 Gm. (1½ grains) of mercuric salicylate (N.F.).

IODIDES

The iodides of sodium or potassium are useful adjuncts in the treatment of late syphilis. Large doses are administered in the various tertiary and late secondary manifestations. They give marked relief, and seem to promote resolution of the gummatous lesions, thus exposing the spirochetes to the action of other drugs or to the natural defense mechanisms of the body.

Potassium iodide is traditionally preferred although it has no advantage over the sodium salt. They are given freely diluted with water or milk an hour after meals. The doses for syphilis are quite large, beginning with 1.5 Gm., per day, increasing by 0.3 Gm. every second day to a total of 7 Gm. per day. Infants tolerate large doses.

Preparation

Potassium Iodide, *Potassii Iodidum,* U.S.P. KI. *Dosage:* 0.3 Gm. (5 grains); antisyphilitic, 2 Gm. (30 grains).

PENICILLIN

Penicillin, if properly administered, is the drug of choice in the treatment of early syphilis. It will cure the vast majority of patients with primary and secondary syphilis. An obvious advantage of penicillin is that practically all patients are willing to complete the treatment. In late syphilis the results are also good. The abnormal spinal fluid is improved, benign gummas, skin, bone, and vascular lesions heal in twelve to sixty-four days with the dosage of 300,000 units.

Penicillin was adopted as the drug of choice for the treatment of early syphilis in our army (European Theatre) on June 26, 1944. A unit dose of 40,000 being given at three-hour intervals for seven and a half days to give a total dosage of 2,400,000 units.

There is considerable difference of opinion regarding the advisability of administering penicillin with arsenic and bismuth in the early stages of syphilis. The majority believe penicillin might be best administered alone and that bismuth and arsenic be reserved for use in treating relapsing cases.

Numerous studies have produced remarkable results regarding the prevention of syphilis in the fetus through treatment of the pregnant mother.

Satisfactory results have been reported from the use of penicillin in *early congenital syphilis.* Platou et al. (1947) brought together observations on two hundred and fifty-two infants. Satisfactory results were attained with 73 per cent, unsatisfactory with 9.1 per cent; in the remaining 17.9 per cent the results were uncertain at the time of the report. Late congenital syphilis, according to reports, responds to penicillin treatment in varying degrees. The same treatment is given for this condition as late infection in adults.

In *cardiovascular* syphilis penicillin is inadvisable because of the sharp Herxheimer reactions which may follow its use. Few benefits have been reported from its use in this condition.

Neurosyphilis: Penicillin causes striking improvement in meningovascular syphilis. In *paresis,* when used with bismuth and tryparsamide, it appears to be of value. In optic atrophy penicillin is useful when employed with fever therapy.

(See Antibiotics, for principal preparations of penicillin.)

TREATMENT OF SYPHILIS

Syphilis, a venereal disease caused by *Treponema pallidum,* has three recognized stages: a primary stage characterized by a chancre, during which there is a widespread dissemination of the organisms throughout the body. There is a secondary stage with skin and mucous membrane lesions. The third stage is characterized by granulomatous lesions, and the more serious cardiovascular and central nervous system involvement.

Early Syphilis

Many plans of treatment have been recommended for syphilis. The Army Treatment for *early syphilis* (1944) is as follows:

1. Mapharsen by vein twice a week for twenty injections.
2. Simultaneously bismuth subsalicylate in oil intramuscularly once a week for five injections.
3. Beginning the eleventh week bismuth subsalicylate once a week for six doses, omitting mapharsen for six weeks.
4. Seventeenth to twenty-sixth week, mapharsen as in first course.
5. Beginning twenty-second week, bismuth weekly for five doses.

Recently, several accelerated schedules were tried, all using the same total quantities of specific drugs as in the long treatments. It was found that when treatment was compressed into periods of less than one or two weeks, the mortality from toxic reactions was excessive. Intermediate schedules were tried in which treatment was given in ten to twelve weeks. These schedules were proved highly successful and probably represent the most desirable program of treatment not involving the use of penicillin.

Accelerated ten- to twelve-week treatment:

1. Oxophenarsine hydrochloride by vein in dose of 60 mg. three times a week for twelve weeks.
2. Simultaneously, a bismuth preparation such as bismuth subsalicylate in a dose of 1.5 cc. (85 mg. bismuth) intramuscularly once weekly.

Penicillin alone:

1. Forty thousand units of penicillin, by the intramuscular route, every three hours for seven and a half days. (Total dose 2.4 million units.)

Latent Syphilis

Latent syphilis refers to a positive Wassermann discovered more than four years after the initial infection plus a negative spinal fluid and no demonstrable lesions. Persons over fifty years of age are usually not treated. Younger persons may be given alternating courses of a heavy metal and an arsenical for one year. (As described for early syphilis.) The bismuth course should precede the arsenic to lessen the chances of a Herxheimer reaction. Use penicillin if patient is sensitive to arsenic. Give a large total dose of six million units over a period of two weeks.

Late Syphilis

Late syphilis refers to the occurrence of symptoms more than four years after the initial infection. The treatment instituted depends on the organ or type of tissue involved.

Treatment is started with a heavy metal (usually bismuth) followed in alternation by an arsenical compound. Use small doses for first course—usually one-half of that used in early syphilis. Continue treatment as recommended for latent syphilis.

Some recommend that penicillin be reserved for those patients sensitive to arsenic and to their unresponse to arsenic treatment. Gummas, however, respond rapidly to penicillin. Potassium iodide, as an adjuvant treatment, accelerates the disappearance of gummatous lesions. Give 0.3 cc. of a saturated solution of potassium iodide three times a day.

Cardiovascular Syphilis.—If there is no congestive heart failure, administer twenty weekly injections of bismuth (one-half dose described for early syphilis). Follow by ten weekly injections of oxophenarsine hydrochloride (dosage 10 to 20 mg.). The latter treatment depends on the individual patient. Treatment may be continued in alternating course for two years, and then be given for one month out of every year thereafter.

Penicillin has not proved particularly successful in this condition. Severe Herheimer reactions may follow its use.

Neurosyphilis.—In *asymptomatic syphilis* of the central nervous system alternate heavy metals and arsenic therapy as described for late syphilis.

Investigators at Johns Hopkins, Moore and Mohr (1946), found a combination of malaria therapy with the use of penicillin effective in the treatment of this condition. The favored dosage was 4,000,000 units of penicillin in fifteen to twenty-five days.

Tabes Dorsalis.—Reynolds (1947) summarized the investigations at Johns Hopkins Hospital. It was found that penicillin relieved many of the distressing symptoms. Since many of the patients are frequently poor fever risks, penicillin alone is probably excellent treatment for this condition.

Alternate Treatment.—Elderly patients may be left untreated if the condition is quiescent; but if the disease is progressing, the following treatment may be given: Start with alternating course of bismuth and arsenic compounds, injections being given every five days. The treatment may be augmented by courses of tryparsamide. Tryparsamide is given in doses of 3 Gm. intravenously once a week for two or three months. Examine eyes periodically for signs of optic atrophy. Continue above treatment for at least one year.

Paresis.—Reynolds et al. (1946) found the results of penicillin-malaria combination superior to penicillin alone. In some debilitated patients, however, the administration of penicillin alone is preferred.

Alternate Method.—Treat by fever therapy followed by simultaneous courses of tryparsamide and bismuth as required. Penicillin should always be given concomitantly with fever. (Fever therapy should be given in a hospital by experienced physicians. Diathermy, hot air cabinets, hot blankets, foreign protein inoculations or malaria inoculations may be used.)

Meningovascular Syphilis.—Penicillin may be used in this condition with good results.

Syphilis in Pregnancy.—Treat vigorously as in early syphilis. If the disease is in a late stage, a short course of bismuth should precede arsenical compounds to lessen the danger of Herxheimer reaction.

Penicillin seems particularly suitable for employment in syphilis of pregnancy. It may be given in a single course over a short period; toxic manifestations are not serious. It cures the disease in the mother, at least in the early stages, and at the same time prevents transfer of the disease from the mother to the fetus. *Dosage:* A course of 2.4 million units early in pregnancy (third month) repeated again about the seventh month.

Congenital Syphilis.—Early congenital syphilis may be treated like early adult syphilis, with arsenical compounds and heavy metals. When intravenous injections are contraindicated, bismuth sulfarsphenamine or sulfarsphenamine may be used intramuscularly. *Dosage:* Neoarsphenamine, or sulfarsphenamine—age two weeks, 30 mg.; three months, 0.1 Gm.; two years, 0.2 Gm.; eight years, 0.4 Gm. to 0.5 Gm. Bismuth sulfarsphenamine doses are about one-half of neoarsphenamine.

Penicillin.—Platou et al. recommend a total dosage of at least 100,000 units per Kg. (2.2 pounds) body weight. The total amount should be divided so that it may be given in equal intramuscular injections every three hours for a period of fifteen days.

Late congenital syphilis may be given the same treatment as late infection in adults. Penicillin may be used with good response in many instances. The total dosage of 40,000 units of penicillin per Kg. (2.2 pounds) of body weight in seven and one-half days.

ANTIMALARIAL DRUGS

Malaria is a recurrent febrile disease caused by infection with various species of *Plasmodia* and transmitted by the *Anopheles* mosquito. Malaria is the most important disease with which mankind has to contend, because it kills more people than any other known disease. The three outstanding species of Plasmodia capable of infecting human beings are *P. falciparum*, *P. vivax*, and *P. malariae*. *P. falciparum* causes the most malignant type, estivo-autumnal malaria, and at the same time is most responsive to treatment. Infections of *P. malariae*, which causes quartan malaria, are relatively infrequent.

P. vivax causes benign tertian malaria. It is a debilitating disease characterized by chronicity and a low mortality rate. With the possible exception of pamaquine and its derivatives, no drug is entirely effective in the prophylaxis or cure of this infection. A suppression of the symptoms, however, may be obtained with various types of the antimalarial drugs.

The antimalarial drugs of importance include the following: quinine, quinacrine, pamaquine, and the newer drugs: chloroquine, paludrine, pentaquine, and chlorguanide hydrochloride.

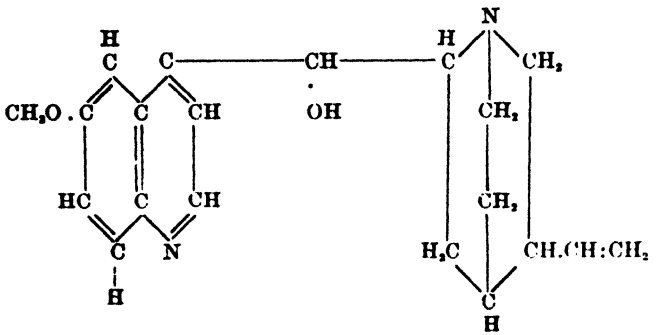
QUININE

Quinine, the chief alkaloid of cinchona, the bark of the cinchona tree was isolated in 1820. It has rapidly replaced crude cinchona preparations in the treatment of malaria. Quinine has a long and interesting history. It was introduced in Europe by members of the Jesuit brotherhood under the name cinchona. It originally received the name cinchona, according to the story, from the Countess of Cinchon (1638), the wife of the governor of Peru, who was cured of a fever by its administration. "Jesuit bark" was one of the names later attached

to this drug. Later medical history contains much on the use of quinine in the treatment of fevers. Binz suggested that quinine acted by killing the organism which causes malaria, which we now know is the malarial plasmodium.

Many derivatives of quinine have been synthesized. The action of quinine practically represents that of cinchona, as well as those of the other cinchona alkaloids. The most important alkaloids of the cinchona group are two pairs of isomers *quinine, quinidine, and cinchonines,* and *cinchonidine.* Since quinine is the most important of the group, and since its physiological effects are so representative of the group, it will be discussed in detail.

The structure of quinine is shown in the following formula:



Quinine

Pharmacological Action.—*Absorption and Excretion.*—Quinine is readily *absorbed* when given by mouth or subcutaneously, appearing in the urine within twenty minutes after oral administration. It continues to be *excreted* in fairly large amounts for twenty-four hours. About one-third is excreted in the urine, and the rest is apparently destroyed by the tissues. In the blood the maximal amount of quinine is present between three and six hours after ingestion.

When given in continuous doses by mouth the concentration in the blood may be from 3 to 10 mg. per liter. Doses of 2 Gm. per day usually result in a concentration of 10 mg. per liter of blood. When the concentration in the blood rises above 10 mg. per liter, symptoms of poisoning usually appear.

Quinine, according to animal experiments, is *distributed* very unevenly in the body. The blood, muscle, and nervous tissue retain little of the drug. The liver, spleen, kidney, and lung concentrate the drug in the largest amounts. Plasma and red blood cells concentrate the drug from two to ten times the amount found in the plasma.

Local Action.—When administered subcutaneously quinine solutions are painful and may cause abscess formation. When taken by mouth, large doses may cause nausea and vomiting. Double salts of quinine and urea hydrochloride are less irritant than other salts and, like quinine salts, produce local anesthesia.

Action on Protoplasm.—Quinine differs from most alkaloids in that it acts not on specialized forms of living matter but generally, on all forms of protoplasm. Quinine is more of a general protoplasmic poison, producing first a transitory stimulation, followed by depression and death.

Antiseptic Action.—Bacteria and yeasts are destroyed at approximately 5:1,000 concentration. The germicidal action equals about one-half that of phenol; and the antiseptic action is about that of mercuric chloride, according to McDonald (1915).

Antimalarial Action.—Quinine is not directly plasmodicidal since higher concentrations of the drug are needed to kill the parasite *in vitro* than *in vivo*. Many theories have been advanced to explain the mode of action of quinine. Regardless of the mechanism of its action, quinine cures the acute symptoms by depressing multiplication of plasmodia in the body and stimulating some of the parasites to change to the sexual form which cannot cause the disease in man.

Action on Leucocytes.—The poisonous effects on leucocytes occur at a concentration of 1:3,000, which is higher than can be obtained in the blood of a living animal. The phagocytic power of leucocytes and the bactericidal powers of the plasma may be lessened slightly by therapeutic doses.

Analgesic Action.—Quinine resembles the salicylates and related drugs in possessing analgesic action. This action is especially valuable in treating pain arising in muscles and joints. The site of action is central.

Action on Central Nervous System.—Moderate doses of quinine cause little action on the central nervous system. Large doses produce cinchonism which is characterized by depression, giddiness, headache, sensation of fullness in the head, deafness, tinnitus, amblyopia, and confusion. The tinnitus seems to be due to congestion of the middle ear and labyrinth or to nerve stimulation. The amblyopia is thought to be due to contraction of the retinal vessels. The sensation of fullness in the head has been interpreted as denoting a dilation of cerebral vessels.

Antipyretic Action.—Therapeutic doses of quinine have little effect on normal temperature. In the presence of fever, however, a distinct antipyretic effect is exerted. The antipyretic mechanism was thought to be due to diminished nitrogen metabolism (Gottlieb), but Barbour and Wing have demonstrated a central action of quinine by application of the drug on centers near the corpus striatum. Hardikar found that quinine acted like other antipyretics, acting on the heat centers of the brain. In malaria, however, destruction of the organic cause of the pyrexia is undoubtedly the chief factor in the antipyretic action.

Respiration.—Respiration is much affected by quinine as is the circulation. Poisonous doses, administered subcutaneously, kill by paralyzing the respiratory centers; the heart action is weakened. Poisonous intravenous doses, however, may produce death by direct cardiac paralysis.

Action on Circulation.—Quinine in therapeutic doses tends to increase slightly the cardiac rate and raise the blood pressure, an action thought to be due to direct action on the heart muscle and the walls of the blood vessels. With large doses the excitability of the heart muscle is depressed. Toxic doses lower the blood pressure by cardiac depression and vasodilatation through peripheral action.

Action on Muscle.—Striated Muscle: There is a transient increase in muscle power followed by a weakness and fatigue. Injections into the muscle lead to necrosis of the fibers. *Unstriated Muscle:* The *uterus* contracts violently when quinine is injected intravenously. It is not reliable in ordinary doses for starting labor pains. Its use in malaria may cause abortion due to its action on the uterus. The action on the uterus is, no doubt, directly on the muscle and is more prolonged than the action caused by ergot, but it is not as strong and reliable as that produced by pituitrin.

Alimentary Tract.—When taken orally, quinine or cinchona preparations act as "bitter tonics," that is, improve the appetite, increase the flow of saliva and gastrointestinal secretions, and tend to excite peristalsis. Excessive doses are irritating.

Metabolism.—Quinine ingestion diminishes destruction of the body proteins. Initially, there may occur increased elimination of nitrogenous products in urine, but this is followed by a decrease which may amount to 39 per cent of the total nitrogen elimination.

Action on Organs of Special Senses.—Moderate doses may disturb hearing, manifested by ringing in the ears, and not infrequently a slight degree of deafness. Large doses may produce dizziness and ataxia due to vestibular involvement. Involvement of the eye, evidenced by disturbance of color vision and contraction of the visual field, is common. These disturbances may be accompanied by narrowing of the lumen of retinal vessels and by pallor of the optic disc. The cause of these sense disturbances is thought to be due to direct action on the nervous structures themselves. Some of the effects may be due to changes in vascular caliber, with or without the accompaniment of hemorrhage.

Toxicology.—Severe results following quinine therapy are rare. Some of the side reactions of quinine have been mentioned under the pharmacological action of quinine. The most common symptoms of toxicity are the sensation of fullness in the head, ringing in the ears, and slight impairment of hearing. Other effects, such as skin eruptions, visual disturbances, vertigo, and temporary blindness are not uncommon. Gastric pain and vomiting may be produced by moderate doses of quinine. Diarrhea or constipation often accompanies quinine therapy. Many individuals have an *idiosyncrasy* to quinine, and the above-mentioned results appear even with a few grains of the drug. The effect of quinine administration in pregnant women is in doubt. In the Far East the opinion prevails that quinine predisposes to abortion.

Skin eruptions due to quinine may appear in various forms, the most common being erythematous, scarlatiniform, or urticarial. Itching is a common complaint. A hemorrhagic tendency may follow the use of quinine and may be distinguished with difficulty from hemorrhage due to malaria itself.

In large doses, 2 to 4 grams (30 to 60 grains) of quinine may produce, in addition to the above symptoms, a delirium resembling that caused by alcohol.

The *fatal dose* of quinine sulfate is approximately 20 grams, of quinidine sulfate, 10 grams, and of plasmochin, 5 to 30 grains. The poisoning causes a congested and hemorrhagic condition of the organs.

TREATMENT: Cinchonism is best treated by caffeine or coffee. Mild symptoms are common and require no treatment. In fact if no symptoms appear, one wonders whether the drug is being well absorbed. It is well to test quinine sensitivity by giving a test dose of 0.6 Gm. (10 grains) before a subject goes to a malarial district.

Remove the poison by lavage (potassium permanganate 0.1 per cent, 1:1,000), emesis, or purging. Administer epinephrine intravenously or intracardially, if necessary. Repeated instillations of atropine solution into the conjunctival sac aid in preventing optical injuries. Administer caffeine or digitalis hypodermically. If excitation persists, give barbital by mouth. Full doses of sodium or potassium bromide will sometimes prevent both tinnitus and headache. *In all cases atabrine must be promptly substituted for quinine if cinchonism appears.*

Therapeutic Uses.—The most important therapeutic use of quinine is in malaria. The treatment of malaria is made difficult because the different species of plasmodia do not respond similarly to drug therapy. The gametocytes and schizonts manifest different chemotropisms, individuals vary in their response to quinine, and the chronicity of the infection is an important factor. As a rule early infections respond relatively easy to therapy as compared with chronic malaria. Relapses are frequent. Early and intensive treatment is indicated. A knowledge of the species of infecting plasmodium is necessary in order to administer the correct treatment.

Quinine in Malaria.—Until recently, quinine was the drug of choice in the treatment of malaria. Since we have three excellent synthetic antimalarial agents in chloroquine, paludrine, and quinacrine, we must admit that quinine is of relatively less importance. It is, however, a valuable adjunct in the treatment of malaria.

If quinine is to be used for the treatment of malaria, it should be given in doses of 10 grains three times daily for two days, then 5 grains morning and night for the ensuing five days.

At a meeting of the Subcommittee on Tropical Diseases of the National Research Council, the following program of dosage was endorsed as an efficient routine of therapy:

1. *Combined Q.A.P. Treatment.* (Method of Choice.)

(a) *Totaquine or quinine sulfate,* 0.64 Gm. (10 grains) three times daily after meals for two or three days or until pyrexia is controlled. Then give

(b) *Quinacrine hydrochloride* (Atabrine), 0.1 Gm. (1½ grains) three times daily after meals for five days. Then after two days without antimalarial medication give

(c) *Pamaquine naphthoate* (Plasmochin), 0.01 Gm. (⅙ grain) three times daily after meals for five days, except for the debilitated patient, who should receive only two doses daily. (Discontinue if toxic symptoms occur. Never give atabrine and plasmochin concurrently.)

QUININE PRESCRIPTIONS

For malaria:

℞

Quinine Sulfate Capsules (5 gr.) ----------No. CL
Sig.: Take as directed.

When the administration of capsules is not advisable (children usually cannot swallow a capsule as easily as an adult), the drug may be prescribed in powder to be mixed with some flavored syrup at the time of administration, or it may be prescribed in liquid form. Syrup of Prepared Cacao, N.F., is an excellent vehicle to use in the prescribing of quinine.

For child (30 pounds):

℞

Quinine Sulfate ---------- 8.40 Gm. (gr. cxxx)
Cacao Syrup ----------q.s. ad 320.00 cc. (f℥viij)
M. Sig.: Teaspoonful as directed (shake well).

Quinine in Other Conditions

***Febrile Conditions.*—Quinine, in doses of 1 to 2 grams (15 to 30 grains) given in the course of an hour, has been used for reduction of temperature in typhoid and typhus fevers, and in fever of pulmonary**

tuberculosis; however, the action is weaker than that provided by coal-tar drugs.

In Inflammatory Conditions.—In *acute coryza* or in *acute tonsillitis*, 0.6 gram (10 grains) of quinine, combined with Dover's powder, will, if given early, abort attacks. *Influenza* responds well to quinine in doses of 0.5 gram (8 grains) daily. In the later stages of chronic cases of *whooping cough*, quinine in doses of from 0.2 to 0.6 gram (3 to 9 grains) tends to arrest coughing spells. In *chronic bronchitis* with profuse secretions, quinine has been recommended. Quinine, though inferior to the salicylates, gives relief to *acute rheumatism* and related conditions.

For treatment of coryza:

℞

Belladonna Extract	0.03 Gm. (gr. ss)
Camphor	0.40 Gm. (gr. vj)
Quinine Sulfate	0.80 Gm. (gr. xij)
Ipecac and Opium Powder	2.00 Gm. (℥ss)

Mix and make 12 capsules.

Sig.: One every half hour for four hours, then one every three hours.

Bitter Tonic and General Stimulant.—Tonic effects are obtained with doses of 0.03 to 0.13 gram (½ to 2 grains) of quinine, three times daily.

Antiseptic and Astringent.—A 1 per cent solution of quinine sulfate is valuable as an antiseptic and stimulant in caring for certain *wounds* and *ulcerations* which are slow to heal. Internally, the antiseptic and astringent actions of quinine are utilized in the treatment of *amebic dysentery* and *cholera*.

As Local Anesthetic.—Solutions of the double hydrochloride of quinine and urea, ranging in strength from 0.25 to 4 per cent, are commonly used for surface anesthesia. The anesthetic action is thought by some to be due to coagulation of the protoplasm of the peripheral nerves. In 2 to 4 per cent solutions the drug exerts a decided hemostatic effect, especially on capillaries.

Quinine and Urea Hydrochloride possesses a low toxicity and produces a long period of local anesthesia. The drug has been used in operations about the anus, on the tonsils, as an anesthetic in cystoscopy, for the removal of small benign tumors, and in many other similar conditions.

Oxytocic and Emmenagogue.—Quinine has been used in the treatment of uterine inertia. It will excite the already acting uterus, but has no specific action in initiating uterine contractions (Cadwallader). In nervous patients quinine may be best given in full doses combined with a sedative, such as a bromide.

In *amenorrhea*, small doses of quinine have been used with some success in stimulating the menstrual flow.

TOTAQUINE

Totaquine is a mixture of alkaloids from the bark of *Cinchona succirubra* Pavon and other suitable species of cinchona. It contains not less than 10 per cent of anhydrous quinine, not less than 25 per cent of cinchonidine and anhydrous quinine combined, and a total of not less than 70 per cent of cinchonidine, cinchonine, anhydrous quinidine, and quinine. It is a yellowish white powder, odorless, has a

bitter taste, almost insoluble in water, but is soluble in warm alcohol and in chloroform. It is more pleasant to take than quinine and many claim that it is equally as effective. It is said to be more irritating to the stomach, and more prone than quinine to produce headaches. The drug is much less expensive than quinine and thus finds a wider use.

PREPARATIONS

Quinine Ethylcarbonate, *Quininae Aethylcarbonas*, U.S.P. (Equinine). *Dosage:* 1 Gm. (15 grains). *Quininae et Aethylis Carbonas*, B.P. *Dosage:* 0.1-1 Gm. (1½-15 grains).

Quinine Bisulfate, *Quininae Bisulfas*, U.S.P. (Quinine Acid Sulfate). *Dosage:* 1 Gm. (15 grains). B.P., 0.06-0.6 Gm. (1-10 grains).

Quinine Dihydrochloride, *Quininae Dihydrochloridum*, U.S.P. *Dosage:* 1 Gm. (15 grains). B.P., 0.06-0.6 Gm. (1-10 grains).

Quinine Sulfate, *Quininae Sulfas*, U.S.P. *Dosage:* 0.6 Gm. (10 grains). B.P., 0.06-0.6 Gm. (1-10 grains).

Quinine Sulfate Tablets, *Tabellae Quininae Sulfatis*, U.S.P. Usual sizes contain 0.1 Gm., 0.2 Gm., or 0.3 Gm.

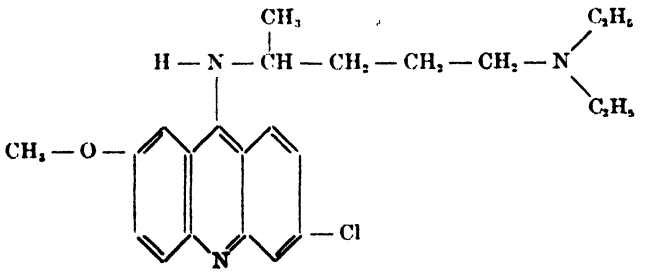
Quinine Hydrochloride, *Quininae Hydrochloridum*, U.S.P. *Dosage:* Oral 0.6 Gm., intramuscular 0.2 Gm. (3 grains).

Quinine and Urethane Injection, *Injectio Quininae et Urethani*, U.S.P. (Quinine Hydrochloride and Ethyl Carbamate Injection, U.S.P. XII). A sterile solution in water, two parts of quinine hydrochloride and one part of ethyl carbamate. *Dosage:* The initial injection should be limited to 0.5 cc. of the solution containing 13 per cent quinine hydrochloride and 6.5 per cent ethyl carbamate to determine idiosyncrasy. The average injection is 1 cc. and should not exceed 2 cc. The total injection at all sites should never exceed 5 cc. of the solution referred to. Intervals between series of treatments should not be less than two or three days.

Totaquine, *Totaquina*, U.S.P., B.P. *Dosage:* 0.6 Gm. (10 grains).

QUINACRINE HYDROCHLORIDE (ATABRINE)

Quinacrine hydrochloride, or atabrine, a synthetic substance of an acridine dye nature, was developed in 1933. It is the hydrochloride of an alkyl amino-acridine derivative. It is a yellow, bitter substance; soluble in water (1:30). Its structural formula is as follows:



Quinacrine

Pharmacological Actions.—*Actions and Uses.*—Quinacrine destroys the asexual forms of the organisms causing malaria and checks the progress of the disease as effectively as quinine. Continual daily

administration does not prevent infection but suppresses development of the cycles until the administration is stopped.

Quinicrine is rapidly absorbed from the intestinal tract and is stored in the tissues for some time, including the skin. It is distributed unevenly in the various tissues, being especially low in the blood and plasma. Quinacrine has cumulative action. Following administration, less than 5 per cent of the drug is excreted. It is excreted by the urine and somewhat by bile. The urinary excretion starts within fifteen minutes and proceeds slowly. Traces of the drug may be found in the urine for one or two months after therapy.

Toxicology.—The most common side effects are dizziness, headache and mild gastrointestinal disturbances, nausea, vomiting, and occasionally diarrhea. It causes harmless discoloration of the skin and urine. Allergic manifestations are encountered but are rarely severe. Toxic psychoses and aplastic anemia are rarely seen.

Therapeutic Uses.—*Use in Malaria.*—Quinacrine is generally superior to quinine, both for suppression and for clinical treatment. Widespread clinical attacks of *P. falciparum* were practically eliminated by its use in the U. S. Army. Recently, however, newer synthetics have been developed which may supersede it in the therapy of malaria.

The treatment recommended by the Surgeon General of the Army, September, 1945, is: (1) *In uncomplicated cases,* quinacrine hydrochloride 0.2 Gm. (3 gr.) with sodium bicarbonate 1 Gm. (15 gr.) in 300 cc. of water every six hours for five doses, followed by 0.1 Gm. (1½ gr.) three times a day for six days; then 0.1 Gm. once a day for ninety days to prevent relapse. If quinacrine is not tolerated, which is seldom, quinine or totaquine 1 Gm. (15 gr.) three times a day for two days followed by 0.6 Gm. (10 gr.) three times a day for five days; then 0.6 Gm. a day for ninety days. Totaquine is more likely to cause gastric upset than quinine. (2) *With persistent vomiting, cerebral symptoms, or a high count of falciparum* in the blood; (a) Quinacrine 0.2 Gm. (3 gr.) in 5 cc. of water *intramuscularly* in each buttock every six or eight hours for three or four doses. As soon as possible, quinacrine by mouth, the total dosage in forty-eight hours being 1.3 Gm. (20 gr.). Then 0.1 Gm. (1½ gr.) three times a day for five days. (b) At the same time quinine dihydrochloride 0.6 Gm. (10 gr.) in 300 to 400 cc. of physiological salt solution is given *intravenously* very slowly indeed (in 30 to 60 minutes) and repeated in three or four hours.

Quinacrine dosage: For treatment of an acute attack, usually 1.0 Gm. of quinacrine hydrochloride is given in divided doses the first day, followed by 0.3 Gm. per day for six days. The action by mouth occurs promptly, so parenteral administration is usually unnecessary. If vomiting occurs, administer by rectum or intramuscularly. *The intravenous route should be avoided.* See treatment for malaria for additional information.

PREPARATIONS

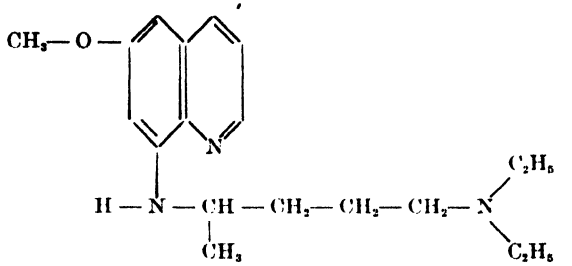
Quinacrine Hydrochloride, *Quinacrinae Hydrochloridum,* U.S.P. *Dosage:* 0.1 Gm. (1½ grains).

Quinacrine Hydrochloride Tablets, Tabellae Quinacrinae Hydrochloridi, U.S.P. The usual sizes contain 50 mg. and 100 mg.

PAMAQUINE

Pamaquine or pamaquine naphthoate contains about 44 per cent of 6-methoxy-8-(1-methyl-4-diethylamino) butylaminoquinoline and about 55 per cent methylene-bis-β-hydroxynaphthoic acid. It is a yellowish, odorless and tasteless powder having a local anesthetic effect

when placed on the tongue. It is insoluble in water, but is soluble in alcohol. The structural formula is:



Pamaquine

Action and Uses.—Its antimalarial properties affect chiefly the gametocytes or sexual forms. Pamaquine appears to have a definite effect in lowering the relapse rate in *P. vivax* when given in large doses and in conjunction with quinine. The toxic effects, however, are so serious as to almost contraindicate its use.

Pamaquine naphthoate should be administered only when it is important to destroy gametocytes, especially of malignant or subtertian malaria. The dose should not exceed 0.02 Gm. by mouth three times a day after meals. It is continued for one week, provided no cyanosis or other toxic reactions appear. Patients should be under constant medical supervision.

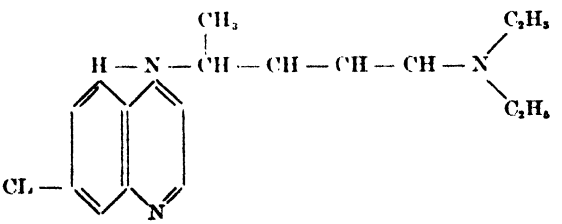
Toxicology.—The usual symptoms following its use are nausea, anorexia, epigastric tenderness, diarrhea, arrhythmia, headache, pallor, subnormal temperature, and changes in the blood, such as methemoglobinemia, cyanosis, hypoglycemia, and jaundice. Because of both its therapeutic limitations and toxic tendencies pamaquine is being rapidly replaced by pentaquine.

PREPARATION

Pamaquine Naphthoate, *Pamaquinae Naphthoas*, N.F. (Aminoquin Naphthoate, Plasmoquin). *Dosage:* 20 mg. (⅓ grain).

CHLOROQUINE

Chloroquine, another very promising new synthetic antimalarial drug, was introduced in 1944. The structural formula is:



Chloroquine

This drug is rapidly absorbed from the gastrointestinal tract, and from 10 to 20 per cent is excreted in the urine.

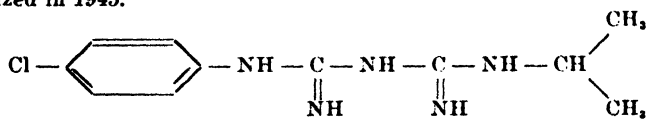
Toxic reactions of chloroquine are similar to those of quinacrine, but occur less frequently. It does not cause yellow coloration of the skin. A mild pruritis may occur.

Chloroquine is effective against the erythrocytic forms of vivax and falciparum plasmodia. Its potency is about three times that of quinacrine. A single dose (500 mg. or less of chloroquine diphosphate) per week gives adequate suppression of symptoms. Chloroquine provides the most rapid rate of parasitic clearance from the blood and the longest latent period between attacks.

According to the National Research Council, chloroquine represents a considerable improvement over atabrine or quinine. For suppression of a latent infection two tablets (0.5 Gm.) once weekly given on the same day each week is adequate. For treatment of an acute attack 1.0 Gm. of chloroquine (4 tablets) is given in divided doses the first day, followed by 0.5 Gm. (2 tablets) on each of two successive days. The total dosage is 2.5 Gm. (10 tablets) in three days. Although this regime does not cure, further relapses do not occur for at least two months. No further treatment may be indicated.

PALUDRINE

Paludrine, possessing the following structural formula, was synthesized in 1945.



Paludrine is readily absorbed following oral administration. About one-third of the dose is excreted through the bile and intestinal mucosa and appears in the feces; some is excreted in the urine.

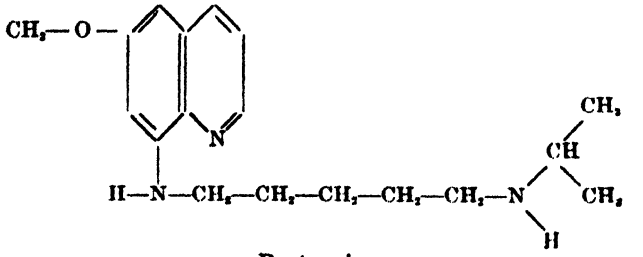
Its ability to suppress symptoms is similar to quinine, quinacrine, and chloroquine, but this action is less rapid, requiring from three to four days. It possesses a very low toxicity, which gives it an advantage over other antimalarial drugs.

Paludrine has a curative effect in *P. falciparum* infections but is without effect on the relapsing rate of *P. vivax* infections. The usual dose is 100 mg. per day. Doses ten times as large produce no toxic reactions.

Paludrine resembles chloroquine in its effectiveness in the treatment of acute attacks of malaria. *Dosage:* 10 to 50 mg. twice daily for fourteen days.

PENTAQUINE

Pentaquine represents another synthetic quinine preparation which is more potent and less toxic than pamaquine. Its formula is 6-methoxy-8-(5-isopropylaminoamylamino)-quinoline, which is written structurally as follows:



Pentaquine

Action and Uses.—Pentaquine is given orally and is rapidly and completely absorbed from the intestinal tract. It is not cumulative. Only small amounts of the drug are excreted, the internal metabolism not being known.

Pentaquine is effective in producing a complete cure in old cases of *P. vivax* infections. It is always used with quinine, and a definite synergistic response results from their use together.

Toxicology.—The toxic manifestations of pentaquine include nausea, abdominal pains, anorexia, anemia, leukopenia, fever, cyanosis, methemoglobin, and jaundice. There is some evidence of synergistic toxic action when given with the sulfa drugs. Lower dosage levels (40 mg.) rarely produce toxic effects and are very effective. Dosage level of 180 mg. per day may cause intravascular hemolysis, postural hypotension, and even syncope.

Therapeutic Uses.—Relapses of infections with *P. falciparum* and *P. vivax* are a major problem in the treatment of malaria. Pentaquine shows considerable promise but is somewhat toxic. *Dosage:* 10 mg. (14 mg. pentaquine diphosphate) together with 0.6 Gm. of quinine sulfate every four hours for two weeks. Paludrine apparently has a similar action, but to a limited degree.

The daily dose is from 40 to 80 mg. of pentaquine monophosphate. The usual course of treatment is fourteen days. A second or third course of treatment may be necessary.

Chlorguanide Hydrochloride

Recent investigations indicate chlorguanide hydrochloride is useful in malaria treatment. It seems evident that 0.3 Gm. of the drug is often essential for the *suppression of malaria*, and for the prevention or *suppression of vivax* malaria (J. A. M. A. 139: 378, Feb. 5, 1949).

MISCELLANEOUS ANTI-INFECTIVE DRUGS

Methenamine

Methenamine, $(CH_2)_6N_4$, hexamethylenamine, hexamine, occurs as small colorless crystals or white powder which is soluble in water (1:1.5) and in alcohol (1:12.5). The drug rapidly decomposes in air and even tablets will lose an appreciable amount of weight. It is of definite value as a urinary antiseptic.

Pharmacological Action.—Methenamine itself is inert and exerts no antiseptic action on tissues except in the urinary tract when the reaction of the urine is acid. When taken by mouth methenamine is *absorbed* rapidly, and the greater part may be *excreted* unchanged by the urine. The excretion starts about one hour after administration and is completed in twelve hours. In the presence of free acid methenamine is decomposed, yielding formaldehyde, which exerts an antiseptic action on urine and on the mucous membrane of the genitourinary tract. Formation of formaldehyde occurs according to the following reaction: The end point depends on the hydrogen-ion concentration.

$$(CH_2)_6N_4 + 6H_2O \rightleftharpoons 4NH_3 + 6HCHO$$

The drugs principally used for acidification of urine have been sodium acid phosphate (NaH_2PO_4), ammonium chloride, and ammonium nitrate, usually in 1 to 1.3 gram doses three or four times daily. The problem of the physician is to maintain the urine at a pH of 5.5 or less. Since chlorphenol red paper or nitrazene paper (Squibb) indicates this degree of acidity, the problem is only to keep the urine at an acidity which will give a positive test with this paper.

Toxicology.—No symptoms arise from therapeutic doses of methenamine, but large doses cause pain and discomfort in the bladder and occasionally hematuria, due to the formaldehyde present. Some patients have an idiosyncrasy to this drug and even small doses may cause painful micturition and frequently hematuria. CAUTION: Hematuria and albuminuria may occur in patients with sensitive or diseased kidneys.

Therapeutic Uses.—Methenamine was one of the most effective urinary antiseptics available until the advent of mandelic acid and more recently the sulfonamides. It is useful in the treatment of ***urinary infections*** (especially *E. coli*), as a ***prophylactic*** against infection in catheterization, and in operations on the urinary organs.

In treatment of pyelitis and cystitis, etc.:

℞

Methenamine ..... 15.00 Gm. (3iv)
Distilled Water .....q.s. ad. 120.00 cc. (f℥iv)

M. Sig.: Teaspoonful every six hours as directed. (Render urine acid with NaH_2PO_4.)

PREPARATIONS

Methenamine, *Methenamina*, U.S.P., Hexamine, B.P. *Dosage:* 0.5 Gm. (7½ grains).

Methenamine Tablets, *Tabellae Methenaminae*, U.S.P. The usual sizes contain 0.3 Gm. and 0.5 Gm.

Mandelic Acid and Its Salts

MANDELIC ACID, $C_6H_5CH(OH)COOH$, is a white crystalline compound soluble in water and alcohol. It was introduced by Rosenheim (1935) as a practically nontoxic keto acid which is excreted unchanged in the urine and renders this bacteriostatic, especially if the reaction of the urine is acid (pH 5-5.5) and the water intake limited. It is often successful against urinary infections which resist sulfonamide treatment. Infections due to staphylococci and *Aerobacter aerogenes*, and possibly colon bacillus infections respond poorly to this drug. Enterococcic organisms (*S. fecalis*) may be treated by mandelic acid derivatives. These infections do not respond to sulfa drugs.

Mandelic acid may be administered as the ammonium, sodium, or calcium salt. The *ammonium salt*, in the form of syrup, is given in doses of 8 cc. four times daily. To avoid nausea it is best to administer this drug following meals and just before retiring. Therapy with ammonium mandelate may not require additional acidifying salts in order to obtain the proper reaction with urine.

CALCIUM MANDELATE, which apparently causes less nausea, is given in doses of 3 Gm. four times a day. With this agent some acidifying agent must be administered. Ammonium chloride in doses of 4 to 8 Gm. is usually sufficient. The reaction of the urine should be followed closely. In some patients proper acidity is difficult to attain.

Toxicology.—The disadvantages of mandelic acid therapy are the large amounts of drugs necessary, tending to gastrointestinal upset and the occasional production of hematuria. Its major drawback is the inability of the damaged kidney to excrete urine of necessary concentration of organic acid or of sufficient low pH or both.

Combined Calcium Mandelate and Methenamine.—In the treatment of nonspecific urinary infections it has been frequently observed that

a combination of calcium mandelate and methenamine, plus an acidifying agent, has proved effective when other forms of therapy have failed.

PREPARATIONS

Mandelic Acid, *Acidum Mandelicum*, U.S.P., B.P. *Dosage:* 3 Gm. (45 grains).

Calcium Mandelate, *Calcii Mandelas*, U.S.P. *Dosage:* 4 Gm. (60 grains).

Chaulmoogra Oil

Chaulmoogra oil has been used in the treatment of leprosy for more than fifty years, and lately for certain types of chronic arthritis. The oil is a fatty substance expressed from seeds of *Taraktogenos kurzii*, a tree growing in Burma and adjacent countries. The crude oils are evil-smelling, irritant substances which cannot be tolerated in therapeutic doses by mouth and are too irritant for intramuscular injection.

Physiological Action.—The therapeutic properties of chaulmoogra oil appear to be due to optically active, unsaturated fatty acids, chiefly chaulmoogric acid and hydnocarpic acid, which occur in the oil as glycerides. These fatty acids apparently destroy the bacillus of leprosy. Some believe that the drug acts by increasing the resistance of the patient rather than by any specific action on the bacillus.

Administration.—The drug is best administered by injection or by mouth, but it may also be administered by inunction. The crude oil, the ethyl ester, and the sodium salts are used, and while the ethyl ester is favored for hypodermic use, the present tendency seems to be in favor of the crude oil.

Rogers recommends a 3 per cent solution of sodium hydnocarpate; to be injected intravenously twice a week, commencing with a dose of 0.2 cc. and gradually increasing the dose to 5 cc. once a week. The formula of Johansen, of the National Leprosarium at Carville is as follows:

Benzocaine	0.2 Gm.
Olive Oil	10.0 cc.
Crude Chaulmoogra Oil	90.0 cc.

Injections of 5 to 8 cc. are made twice a week in the deltoid muscle. Associated with this, the crude oil is given orally, beginning with 0.6 cc. (10 minims) in capsules three times a day after meals, this being gradually increased to 1.2 cc. (20 minims).

Chaulmoogra oil and its derivatives are now considered to be relatively ineffective in the treatment of leprosy. Penicillin and the common sulfonamides may exert a beneficial effect upon secondary invaders. Promin and diasone probably produce some beneficial effect.

PREPARATIONS

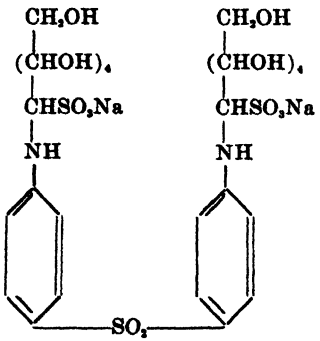
Chaulmoogra Oil, *Oleum Chaulmoograe*, N.F. (Hydnocarpus Oil). *Dosage:* 1 cc. (*Oleum Hydnocarpi*, Hydnocarpus Oil, B.P.).

Ethyl Chaulmoograte, *Aethylis Chaulmoogras*, N.F. *Dosage:* Oral or intramuscular: 2 cc. (N.F.).

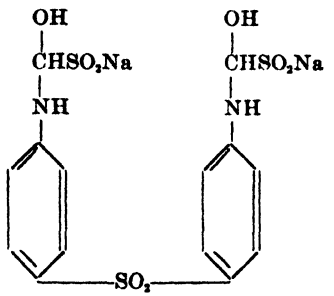
Sulfones

A number of sulfones have given promising results in the treatment of experimental tuberculosis in guinea pigs. Those of special

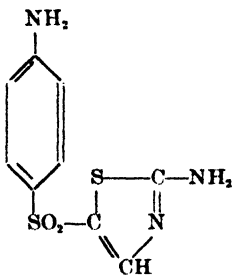
interest include promin, diasone, and promizole. The formulas for these drugs are:



Promin



Diasone



Promizole

Leprosy.—Promin and diasone undoubtedly produce some beneficial effect on the disease. Promin has been given intravenously, daily, in doses of 1 to 5 Gm. with encouraging results. Diasone has been used in doses of 1 Gm. daily by mouth. Objective improvement was observed by Faget et al. (1946) in 65 per cent of patients. Promizole, another sulfone derivative suitable for oral administration, was also used by Faget (1946) with encouraging results.

Tuberculosis.—The sulfones (promin, diasone, and promizole) have a definitely inhibitory effect on tuberculosis in rabbits and guinea pigs. Unfortunately they are toxic; and their effects on human beings have been inconsistent, and beneficial actions have not been comparable to those obtained in animals.

Streptomycin with *promin* and *diasone* have given some encouraging results.

References

Syphilis

Beerman, H., and Wammock, V. S.: Dichlorophenarsine Hydrochloride in the Treatment of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. 31: 150, 1947.

Cutting, W. C.: Manual of Clinical Therapeutics, ed. 2, Philadelphia, 1948, W. B. Saunders Co.

Eagle, H.: The Relative Toxicity and Therapeutic Activity in Experimental Syphilis of Bismuth Subsalicylate, Bismosol and Biliposol, Am. J. Syph., Gonor. & Ven. Dis. **30**: 549, 1946.

Kendell, H. W.: Fever-Chemotherapy, Clinics **4**: 1614, 1946.

Kolmer, J. A., Brown, H., and Rule, A. M.: Studies in the Bismuth Therapy of Syphilis. 1. A Comparative Study of the Toxicity and Therapeutic Activity of Bismuth Compounds Commonly Employed in the Treatment of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **23**: 7, 1939.

Moore, J. A.: The Modern Treatment of Syphilis, Springfield, Ill., 1943, Charles C Thomas.

Probey, T. F., Norris, E. W., Diebert, A. V., and Price, E. V.: Sulfarsphenamine in the Therapy of Syphilis—A Comparative Study of the Toxic Manifestations of Neoarsphenamine and Sulfarsphenamine, Pub. Health Rep. **59**: 733, 1944.

Reynolds, F. W.: Syphilis, J. A. M. A. **131**: 1255, 1946.

Reynolds, F. W., and Moore, J. E.: Syphilis—A Review of the Recent Literature, Arch. Int. Med. **78**: 592, 733, 1945-1946.

Top, F. H.: Communicable Diseases, ed. 2, St. Louis, 1947, The C. V. Mosby Co.

Antimalarial Drugs

Bang, F. B., Hairston, N. G., Trager, W., and Maier, J.: Treatment of Acute Attacks of Vivax and Falciparum Malaria: A Comparison of Atabrine and Quinine, Bull. U. S. Army M. Dept. **7**: 75, 1947.

Board for the Coordination of Malaria Studies of the National Research Council, J. A. M. A. **130**: 109, 1946.

Fitzhugh, O. G., Nelson, A. A., and Calvery, H. O.: Chronic Toxicity of Quinacrine, J. Pharmacol. & Exper. Therap. **85**: 207, 1945.

Hawking, F.: Activation of Paludrine in Vitro, Nature **159**: 409, 1947.

Kelsey, F. E., Oldham, F. K., and Geiling, E. M. K.: Studies on Antimalarial Drugs—the Metabolism of Quinine and Quinidine in Birds and Mammals, J. Pharmacol. & Exper. Therap. **85**: 170, 1945.

Loeb, R. F.: Activity of a New Antimalarial Agent, Chloroquine (SN 7, 618), J. A. M. A. **130**: 1069, 1946.

Loeb, R. F.: Activity of a New Antimalarial Agent, Pentaquine (SN 13,276), J. A. M. A. **132**: 321, 1946.

Most, H., Kane, C. A., Lavietes, P. H., London, I. M., Schroeder, E. F., and Hayman, J. M.: Combined Quinine-Plasmochin Treatment of Vivax Malaria: Effect on Relapse Rate, Am. J. M. Sc. **212**: 550, 1946.

Russell, Paul F., West, Luther S., and Manwell, R. D.: Practical Malariology, Philadelphia, 1946, W. B. Saunders Co.

Schaffer, A. J., and Lewis, R. A.: Atabrine Studies in the Field: I. The Relation of Serum Atabrine Level to Breakthrough of Previously Contracted Vivax Malaria, Bull. Johns Hopkins Hosp. **78**: 265, 1946.

Sipero, J. J.: Malaria Problem Today, J. A. M. A. **132**: 623, 1946.

Wiselogle, F. Y.: A Survey of Antimalarial Drugs, Ann Arbor, Mich., 1941-1945, 1946, Edwards Brothers, Inc.

Sulfones

Faget, G. H., and Pogge, R. C.: The Therapeutic Effect of Promin in Leprosy, Pub. Health Rep. 60: 1165, 1945.

Faget, G. H., Pogge, R. C., and Johansen, F. A.: Present Status of Diasone in the Treatment of Leprosy, Pub. Health Rep. 61: 960, 1946.

Faget, G. H., Pogge, R. C., and Johansen, F. A.: Promizole Treatment of Leprosy, Pub. Health Rep. 61: 957, 1946.

Top, F. H.: Cummunicable Diseases, ed. 2, St. Louis, 1947, The C. V. Mosby Co.

CHAPTER X

DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM

I. STIMULANTS; DEPRESSANTS—GENERAL ANESTHETICS, HYPNOTICS, AND SEDATIVES

The chief function of the nervous system is to enable the various parts of the body to respond to stimuli. If the stimulus is under the control of the consciousness, and can be initiated or stopped at will, it is called *voluntary*. If the responses are not under the control of the will they are termed *involuntary*.

The nervous system may be divided into two main portions:

1. The central nervous system.
2. The peripheral nervous system.

The *central nervous system* consists of the brain and the spinal cord and many thousand sensory, motor, and association nerve fibers. The central nervous system may be divided into four main parts: cerebrum, cerebellum, medulla oblongata, and the spinal cord.

The *peripheral nervous system* consists of thousands of sensory neurons which convey afferent impulses from every part of the body to the central nervous system, and thousands of motor neurons which convey efferent responses from the central nervous system to the various muscles, glands, etc. The peripheral nervous system may be divided into the autonomic system, consisting of the sympathetic and parasympathetic divisions, and the cerebrospinal nervous system. The autonomic nervous system controls the vegetative side of life—nutrition, reproduction, circulation, etc. Almost all of the internal organs receive nerve fibers from this system.

STIMULANTS

STIMULANTS OF CEREBRUM

The chief drugs of the *caffeine group* are *caffeine, theobromine,* and *theophylline.* They possess several characteristic actions: (1) Increased irritability of the central nervous system from above downward; leading to stimulation of the psychic areas, the medullary centers (respiratory, vasomotor, and vagus). (2) Increased ease of muscular contraction. (3) Production of diuresis. (4) Vasodilatation by direct action on vessels. Caffeine is by far the most important central nervous system stimulant of this group.

Caffeine

Caffeine, trimethylxanthine, is an alkaloid obtained commercially from damaged tea leaves, but occurs in a variety of other plants, e.g., coffee, kola, guarana, maté, etc. Coffee contains about 0.67 to 2.25 per cent and tea about 3.2 per cent of caffeine. It is closely related to other methylxanthines, mainly theobromine (3.7 dimethylxanthine) from cacao, and theophylline (1.3 dimethylxanthine) which is usually

prepared synthetically. Xanthine and its methyl derivatives produce the principal actions of the group.

Pharmacological Action.—The main actions of caffeine are: stimulation of all parts of the central nervous system, stimulation of muscle, cardiac and vasomotor stimulation, and finally, stimulation of urine formation. Its actions are complex and not readily controllable.

Caffeine is rapidly *absorbed* from the stomach and intestines following oral administration; the drug is also rapidly absorbed following subcutaneous injections. Cerebral stimulation, following oral doses, occurs in from one-half to one and one-half hours. *Excretion* is fairly rapid, within a few hours. Caffeine loses its methyl group as it passes through the body but forms dimethyl and monomethyl xanthines, xanthine, and urea. Some caffeine remains unchanged. About 10 per cent of ingested caffeine appears in the urine in the form of the above-mentioned decomposition products. The rest is oxidized in the body to urea, carbon dioxide, and water. Most investigators believe that there is no increase in excretion of uric acid in the urine of a normal person, while others find a definite increase in the uric acid content (Benedict).

Action on Central Nervous System.—Caffeine stimulates all parts of the central nervous system from above downward, which includes psychic areas, medullary centers, and the cord. This action may diminish the patient's feeling of exhaustion and improve his sense of well-being. Unlike strychnine, it produces a greater action on the brain centers than on the cord, but like strychnine, it stimulates the vital centers of the medulla.

Cerebrum.—Moderate doses of caffeine (2 to 3 grains) stimulate the entire cerebrum. There is a stimulation of the intellectual centers, especially those of reason, judgment, and self-control. The mind becomes keener and more alert, the spirits higher, and thinking becomes more effective. At the same time the sense of pain becomes more acute and the sense of touch more discriminating. Small doses of caffeine act as a true stimulant of the intellectual and motor centers of the cerebrum, while larger doses (8 to 15 grains) sometimes produce over-excitability, agitation, and inability to concentrate. The stimulation is apparently not followed by depression, except as it exhausts reserves.

In sick persons it is possible that the stimulating effect of caffeine may produce untoward effects, making pain more acute and the patient more restless and alert, thus possessing a keener realization of the seriousness of his illness.

Medulla.—Caffeine strongly stimulates the respiratory center, causing an increase of depth and frequency of the respiration. It has slight action on the vasomotor and vagus centers. This stimulation of the respiratory center is especially evident after morphine, excessive doses of which may exhaust the respiratory system and cause asphyxia.

Spinal Cord.—Caffeine increases the reflex activity of the spinal cord. Therapeutic doses tend to improve the tone of muscle, while large doses may cause twitching of muscles, especially those of the limbs and face.

Action on Circulation.—Caffeine is purely an emergency drug, which may be used effectively as a circulatory stimulant, but should not be administered indefinitely. It acts on the heart and blood vessels, peripherally and centrally. The predominant action of a therapeutic dose is vasodilatation combined with cardiac stimulation. This may raise the blood pressure slightly and favor blood flow. The other purine derivatives, such as theophylline and its compounds, and also theobromine, are

too feeble in their action as cardiac and vasomotor stimulants to be of value in the treatment of circulatory failure.

Heart.—Caffeine, through direct action on the heart muscle, may raise its tone, increase both the strength and completeness of its systole, promote diastole relaxation, and if there is not too much acceleration produced, may result in an increase of cardiac output. Some improvement in coronary circulation, by a specific dilatation, follows the use of caffeine. On the other hand, in susceptible individuals, large doses may produce harmful tachycardia and impair the cardiac output by diminishing diastolic relaxation. Some clinicians feel that in shock the danger of cardiac death is increased by caffeine. It is said by some workers that arrhythmia caused by digitalis may be removed by caffeine.

Arteries.—The vasoconstrictor center is moderately stimulated by caffeine, but in general, peripheral vasodilatation overcomes this effect. A hypodermic injection of 0.3 gram (5 grains) slows the pulse slightly and rarely raises the blood pressure.

Action on the Kidneys.—Caffeine is a diuretic. This is especially true when there is excess fluid in the body. It speeds up the fluid output and increases elimination of urinary solids. Caffeine may act partly by increasing blood flow through the dilated renal arteries, but the major part of the action may be directly on the kidney. The direct action on the kidney is caused by stimulation of the secretory cells of the tubules, and by increasing the permeability and number of active tubules.

Action on the Muscles.—Extensive animal experimentation has shown that caffeine acts directly on striated muscle, increasing its irritability and strength of contraction. These results may occur from direct stimulation of motor areas in the cerebrum. The results from such stimulation are improved muscle tone and lessened susceptibility to fatigue.

Experiments with large groups of soldiers and laborers have revealed that caffeine used in connection with a normal diet will increase the ability to endure prolonged physical exertion. Hyde and co-workers found that non-athletic individuals showed a greater increase in endurance than did the athletes on the same dose.

Action on Metabolism.—Large doses increase metabolism and raise the temperature. In man from 0.5 to 0.7 gram (8 to 10 grains) of caffeine causes an increase in basal metabolism with no significant change in pulse rate, respiratory quotient, and heat loss through evaporation.

Toxicology.—Fatal poisoning by caffeine is rare. A fatal dose may be, presumably, about 10 grams. *Acute Poisoning.* Excessive doses produce insomnia, nervousness, headache, palpitation, nausea and vomiting, especially in susceptible persons. Toxic doses may produce tetanic convulsions and cardiac dilatation. *Chronic Poisoning.* The symptoms of chronic poisoning are exaggerated reflexes, insomnia, anxiety, neurosis, and functional cardiac symptoms. *Treat* by stopping the use of the drug. Evacuants and narcotics (bromide, chloral, etc.) may be indicated in acute conditions.

Idiosyncrasy toward caffeine is apparent in some individuals. Children and nervous and weakened individuals are apparently more susceptible.

Therapeutic Uses.—Caffeine is probably the most widely used drug. It is usually prescribed in the form of citrated caffeine, or caffeine and sodium benzoate. The citric acid and the sodium benzoate are used to render caffeine more soluble. Caffeine and sodium benzoate is used almost exclusively for hypodermic administration. Citrated caffeine is the usual choice for oral administration. The drug may be employed medicinally by giving the beverages tea and coffee. The

average caffeine content of a cup of coffee is about 2.0 grains; the different brands of coffee vary, however, in caffeine content. For example, Mocha coffee contains about 0.67 per cent caffeine while gray Java coffee contains 2.21 per cent. A cup of tea is usually a weaker drink as less tea leaves are used.

Coma and Collapse.—Caffeine is useful in collapse. It is a cerebral as well as a cardiac and respiratory stimulant. Caffeine and sodium benzoate, 7½ grains (0.5 Gm.), should be administered subcutaneously or intramuscularly. As a circulatory stimulant in diabetic *coma* Joslin writes: "... we have made it a rule to use caffeine in the form of caffeine and sodium benzoate freely. The usual subcutaneous dose is 5 to 8 grains (0.3 to 0.5 Gm.) every two hours, but usually less than 40 grains (2.3 Gm.) have been given in any twenty-four hours."

Antidote in Narcotic Poisoning.—Caffeine may be used in narcotic poisoning in the form of hot coffee, which may be administered by rectum if the stomach is to be washed out. It is an efficient antidote for poisoning by opium, salicylates, cyanide, aspidium, alcohol, and other hypnotics. Administer caffeine and sodium benzoate, 7½ grains, intramuscularly or subcutaneously.

Cardiac Diseases.—The cardiac stimulation is useful in temporary cardiac weakness. In cases of cardiac failure in acute infectious diseases caffeine is indicated. It is generally best administered hypodermically in the form of caffeine and sodium benzoate. The average dose lies between 0.3 and 1 gram. Its frequency of administration should be guided by its effectiveness. It should be regarded as an emergency measure.

Diuretic.—Caffeine is a valuable diuretic. It is especially efficient in some cases of dropsy, although it is generally inferior to the other xanthine derivatives.

Roentgen Sickness.—Symptomatic relief may follow the injection of caffeine and sodium benzoate, 0.5 Gm. subcutaneously.

Heat Exhaustion.—Besides the injection of 500 to 1,000 cc. of physiological salt solution, it is advisable to give a stimulant such as caffeine and sodium benzoate, 0.5 Gm. subcutaneously.

Functional Hypoglycemia.—Caffeine in the form of caffeine and sodium benzoate (0.3 Gm.) given subcutaneously is effective in emergencies. A cup of coffee is so effective as to serve in some instances as a diagnostic test (Harris).

Headache.—It relieves some forms of headache, but in the congestive form it may increase the pain. In migraine a capsule of aminopyrine (5 grains) and citrated caffeine (2 grains), administered three or four times in twenty-four hours is often effective.

For headache:

℞

Citrated Caffeine	0.36 Gm. (gr.vj)
Acetophenetidin	2.00 Gm. (ʒss)
Sodium Bromide	6.00 Gm. (ʒiss)

M. div. in chart. No. vi.

Sig.: One powder in water every three hours until relief.

Preparations

Caffeina, Caffeine, U.S.P., B.P. *Dosage:* 0.2 Gm. (3 grains) in capsules.

Caffeine and Sodium Benzoate, *Caffeina et Sodii Benzoate,* U.S.P., B.P. *Dosage:* Oral or intramuscular, 0.5 Gm. (7½ grains).

Caffeine and Sodium Benzoate Injection, *Injectio Caffeinae et Sodii Benzoatis*, U.S.P. A sterile solution in water for injection. It contains an amount of anhydrous caffeine equivalent to 48 per cent and an amount of sodium benzoate equivalent to 51 per cent of the labeled amount of caffeine and sodium benzoate, including all tolerances. The usual sizes contain 0.25 Gm. and 0.5 Gm. in 2 cc.

Citrated Caffeine, *Caffeina Citrata*, U.S.P. *Dosage:* 0.3 Gm. (5 grains).

Theobromine and Theophylline

The central actions of theophylline are less than those of caffeine. The central actions of theobromine are very much weaker. Since the circulatory and diuretic effects of these drugs are correspondingly intensified with the decrease in central effects, these drugs are primarily used for their diuretic effects (See Diuretics).

DRUGS WHICH STIMULATE THE MEDULLA

The drugs which stimulate the medulla include apomorphine, picrotoxin, metrazol, and nikethamide. Metrazol and nikethamide are synthetic medullary stimulants.

Apomorphine

Apomorphine, $C_{17}H_{17}NO_2$, is a synthetic derivative of morphine made by the dehydrating action of concentrated acids upon the alkaloid. It is a white powder slightly soluble in water (1:50) and in alcohol (1:50).

Pharmacological Action.—Apomorphine possesses little narcotic action, but is of importance therapeutically and toxicologically because it produces vigorous vomiting. Nausea comes on promptly and vomiting occurs within one minute and lasts for a few minutes. Larger doses produce vomiting which continues for an hour or more, and may result in collapse. The specific action of apomorphine on the vomiting center was observed by Hatcher and Weiss. They showed that the small amount (0.001 mg.) of apomorphine per kilogram of body weight induced vomiting in dogs when applied directly to the vomiting center. Small doses of apomorphine are expectorant, increasing the fluidity of the bronchial secretions.

Toxic doses of apomorphine induce salivation, lacrimation, weakness, dizziness, and convulsions. *Death* may follow due to respiratory failure, although no such death is on record. *Treatment* should be directed at maintaining respiration.

Therapeutic Uses.—Apomorphine is used chiefly as an emetic and sedative expectorant. *Emetic.*—Emetics are less frequently employed to evacuate the stomach than formerly, as the stomach tube is now preferred. Emesis, however, may be indicated in poisoning, and here apomorphine is indicated. Apomorphine hydrochloride is an excellent emetic in arsenic, oxalic acid, and wood alcohol poisoning. Administer $\frac{1}{10}$ grain (0.006 Gm.) hypodermically. In narcotic poisoning apomorphine may not act, because of the depression of the vomiting center.

Sedative Expectorant.—As a sedative expectorant apomorphine, in a dose of $\frac{1}{60}$ to $\frac{1}{30}$ grain (0.001 to 0.002 Gm.), is advised.

Hypnotic.—Apomorphine may be used as a hypnotic in asthma and delirium tremens. Lambert says that apomorphine hydrochloride, $\frac{1}{10}$ grain (0.006 Gm.), combined with strychnine sulfate, $\frac{1}{30}$ grain (0.002

Gm.), is an excellent sedative in delirium tremens. Apomorphine is recommended as a sedative in hiccup.

Paroxysmal Auricular Tachycardia.—Apomorphine hydrochloride 1/20 grain (3 mg.), will frequently stop paroxysms (Gold, 1940).

PREPARATION

Apomorphine Hydrochloride, *Apomorphinae Hydrochloridum*, U.S.P., B.P. *Dosage:* Emetic, by hypodermic injection, 5 mg. (1/12 grain). Expectorant, 1 mg. (1/60 grain), repeated once an hour or once in two hours.

Picrotoxin

Picrotoxin is a neutral principle of the dried fruit of *Anamirta paniculata*, a climbing shrub of the East Indies. The plant contains about 1 per cent of picrotoxin ($C_{30}H_{34}O_{13}$). The fruit has been used as a fish and bird poison, and as a remedy against parasites and vermin. It is sufficiently soluble to make a 0.3 per cent solution. When chlorbutanol (0.5%) is added it keeps indefinitely.

Pharmacological Action.—Picrotoxin is a powerful central nervous system stimulant. In mammals it stimulates the cortex although its most prominent effect is on the midbrain and medulla. Large doses affect the cord.

One of the most important actions of picrotoxin, first mentioned by Maloney, Fitch and Tatum (1931), is its ability to antagonize the central depression caused by large doses of barbiturates. This drug is the most effective of all central nervous system stimulants in this respect. Picrotoxin increases the rate of respiration, an action which is of value in barbiturate poisoning. It also produces a rise in blood pressure due to stimulation of the vasomotor center.

The drug is rapidly *absorbed* from all channels. Following intravenous administration, it leaves the blood stream in about twenty minutes. It is apparently destroyed quite readily and this accounts for the clinical practice of administering small doses frequently for sustained effect.

Toxicology.—Picrotoxin is a dangerous medullary stimulant because the therapeutic dose is near the toxic dose. The initial symptoms are burning sensation in the mouth, esophagus, and stomach, with salivation, nausea and vomiting, cramps and diarrhea. Following these symptoms are sweating, pallor, headache, palpitation, and shallow respiration, passing into unconsciousness. Convulsions of the tonic and clonic type may occur. Sometimes the jaws close as in strychnine poisoning. *Death* is due to respiratory failure. *Treat* by emetics, chloroform for convulsions, and stimulants in the latter stages.

Therapeutic Uses.—The medullary stimulation produced by picrotoxin might be expected to have many therapeutic uses. Such use is handicapped by the nearness of the therapeutic and toxic doses. The therapeutic dose is from 0.5 to 2 mg.

Analeptic.—Striking results have been obtained by the use of picrotoxin as a restorative, due to the stimulating effect on the vital centers of the medulla. This action may be sufficient to keep the patient alive until the offending poison is removed.

Treatment of Barbiturate Poisoning.—In barbiturate poisoning picrotoxin may be administered in large doses. It must be administered by

vein in divided doses of 3 to 10 mg. (its usual dose is 0.5 to 2 mg.) and the total amount administered should depend upon the response of the patient.

Chorea and Convulsions.—Picrotoxin has been used in chorea and convulsions in children with some success, but such use is not advisable.

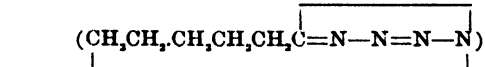
Preparations

Picrotoxin, *Picrotoxinum*, U.S.P. *Dosage:* 2 mg. (1/30 grain) or more depending on severity of barbiturate poisoning.

Picrotoxin Injection, *Injectio Picrotoxini*, U.S.P. Sterile solution of picrotoxin in isotonic solution of sodium chloride. *Dosage:* Intravenous 2 mg. or more (1/30 grain) depending on severity of barbiturate poisoning.

Metrazol

Metrazol, N.N.R., pentamethylenetetrazol (cardiazol)



is a promptly acting circulatory and respiratory stimulant. It is a white crystalline powder prepared synthetically and is very soluble in water. Solutions do not deteriorate on standing and may be sterilized by heat.

Action and Uses.—Metrazol is a powerful stimulant of the central nervous system, especially of the medulla. The vasomotor and vagal centers are likewise stimulated.

Metrazol is rapidly absorbed and likewise rapidly detoxified. In depressed states of the circulation and respiration, metrazol tends to raise the blood pressure toward normal, to improve the pulse, and increase the depth of respiration. It may cause capillary dilatation of the splanchnic region, and animal experiments indicate that intravenous injection may be dangerous.

It is indicated (1) in *circulatory collapse* and *shock* as a restorative; (2) in *respiratory depression* and *deep anesthesia;* (3) to antidote barbiturate and morphine poisoning; (4) in asphyxia neonatorum to stimulate both circulation and respiration. Metrazol is also used in the treatment of *mental disorders* in doses which induce convulsions.

Boyd (1942) reported termination of attacks of *paroxysmal auricular tachycardia* through the intravenous administration of 1 cc. of the commercial ampul preparations of metrazol. In *heart block,* Myres (1941) obtained symptomatic relief using a 1½ grain (0.1 Gm.) tablet three times a day.

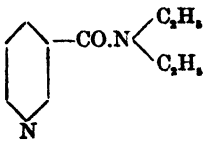
Administration.—*Parenterally*—give 0.1 to 0.3 Gm. (1½-4½ grains) intramuscularly, subcutaneously, or intravenously, repeated as required; in extreme emergencies, collapse or narcosis, inject 3 cc. (10% aqueous solution) intravenously or intramuscularly and repeat this dose if necessary. *Orally*—give 1½ to 4½ grains (1 to 3 tablets) or 1 to 3 cc. of 10 per cent solution several times daily. The action of metrazol is more prolonged following oral administration. It may be combined with digitalis and the xanthine diuretics.

Preparation

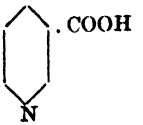
Metrazol, N.N.R. Supplied in ampules, tablets, and powder.

Nikethamide (Coramine)

Nikethamide, N.N.R., is pyridine-β-carboxylic acid diethylamide or diethylamide of nicotinic acid. The following formulas show nikethamide's close relationship to nicotinic acid.



Nikethamide



Nicotinic acid

Action and Uses.—Nikethamide's most striking pharmacological effect is stimulation of the respiration. It also causes a sustained rise in the blood pressure, particularly under those conditions in which lowered vascular tension is due to depression of the central nervous system. In experiments to study the mechanism of this effect, it can be observed that the blood pressure increase is essentially due to stimulation of the so-called vasomotor centers, i.e., those parts of the brain which regulate and coordinate the various factors of circulation.

Nikethamide is *absorbed* from all sites of administration. It is most effective, however, following intravenous injection. The drug has a wide margin of safety, the toxic dose being approximately ten times the therapeutic dose.

Nikethamide has been widely used as a respiratory stimulant in accidents (carbon monoxide, barbiturate, narcotic, etc., poisoning), surgical anesthesia, collapse, alcoholism, asphyxia neonatorum, etc. It is indicated in circulatory depression or failure of central origin, as in traumatic or surgical shock, syncope, acute infections, anesthetic accidents, etc. It is said to improve coronary flow. Nikethamide is also effective in the treatment of pellagra, including all degrees of nicotinic acid deficiency.

Hiccup.—Schell (1947) reported that intravenous injections of 2 to 5 cc. doses of nikethamide stopped attacks in patients with cardiovascular disease.

Administration.—Nikethamide is available in 25 per cent aqueous solution for oral, subcutaneous, intramuscular, or intravenous administration. The drug should be given intravenously in emergencies; no benefit can be expected from oral administration and possibly from subcutaneous administration. When doses larger than 3.0 cc. are given, the administration should be slow and reactions watched for. Large doses may produce convulsions and may cause death from respiratory failure. The dose may be repeated as required.

STIMULANTS OF THE SPINAL CORD

The strychnine group of drugs has some therapeutic and is of considerable toxicological importance. They increase the reflex excitability of the spinal cord and of the medullary centers. This group includes strychnine and brucine.

Strychnine

Strychnine, $C_{21}H_{22}O_2N_2$, is an alkaloid obtained from seeds of *Strychnos nux vomica*, a small tree grown commercially in China and the East

Indies. The grayish disk-shaped seeds of nux vomica were known to be poisonous as early as 1640. Records show that the seeds were used to destroy crows, pests, stray dogs, etc. These seeds yield several alkaloids, principally strychnine and brucine, of which strychnine is the most important. The alkaloid, strychnine, which was isolated in 1820, has largely supplemented the whole drug for medicinal purposes. Strychnine was at one time one of the most frequently used drugs, either as a preparation of the drug or as the alkaloid, but it is now less frequently used. Osler once said that he "practiced medicine with hope and nux vomica." Contrary to Dr. Osler, although strychnine is an interesting drug, it is used to a limited extent in present-day medicine.

Pharmacological Action.—Strychnine increases the reflex excitability of the spinal cord and the medullary centers, but has little effect on the centers above the medulla.

Strychnine is quickly *absorbed* from the intestine. Following oral administration, after hypodermic, intravenous, or rectal administration, absorption is much more rapid. After absorption strychnine is found chiefly in the blood, liver, and kidneys. The drug is destroyed chiefly by the liver, but about 25 per cent is *excreted* unchanged, mainly in the urine. Urinary excretion starts soon after absorption and is completed in from forty-eight to seventy-two hours. When injected into the blood stream, 50 per cent leaves the blood in five minutes.

Action on the Spinal Cord.—The dominant action of strychnine is its ability to increase the reflex excitability of the spinal cord. Practically all reflexes are equally affected. Strychnine acts strongly on the spinal cord, less powerfully on the medulla, and slightly on the brain. Even weak doses intensify the irritability of the spinal reflexes so that weaker stimuli are effective. In a normal animal, irritation usually produces the same movements, that is, certain muscles contract while their antagonists are inhibited. Under strychnine poisoning the simple reflexes are stronger and are elicited by weaker stimuli. If a strong stimulus is applied, a different response results; practically all the muscles contract at once, there being no inhibition by antagonists. This results in the stronger muscles overcoming the weaker. In both cases the change in character arises from the cord. Some explain it as a lowering of the threshold of resistance at the synapses lying between the sensory and motor neurons of these reflexes. A certain resistance in the different paths is essential for coordinate movements, otherwise all muscles would contract at once. The action of strychnine may remove this resistance to the passage of impulses and extend the areas of action over all the muscles, favoring of course the usual path of the impulses.

Convulsions due to strychnine may last one or two minutes followed by five to ten minutes' relaxation. Death occurs during a seizure, due to fixation of the respiratory muscles.

Sherrington suggests that strychnine apparently changes an inhibition into a motor response, and that the apparent reversal might really be due to the exaggeration of a marked component in the inhibitory response.

The stimulation of the spinal cord is followed by depression and paralysis. The sensory part of the spinal cord seems to become paralyzed first, and then the motor cells, until stimulation elicits no action.

Action on Medulla.—There is a difference of opinion concerning the action of strychnine on the medulla. All agree in general that strychnine

in therapeutic doses will resensitize the respiratory center after it has been depressed by narcotics, enabling it to respond to normal stimuli.

Strychnine stimulates the cough centers changing a weak cough to a productive cough.

As the vasomotor centers and the cord are stimulated so the splanchnic vessels are constricted and cutaneous and muscular vessels dilated from stimulation of the vasodilator center. The blood is thus increased in the limbs, skin, lungs, and brain. The brain has little or no vasoconstrictor supply.

Action on the Brain.—The special senses—touch, taste, smell, and hearing—are made more acute. The field of vision is increased and color discrimination is sharpened. Pain is more keenly felt.

Action on the Heart.—The heart is not directly affected by strychnine, although there may occur some slowing due to stimulation of the inhibitory (vagus) center.

Local Action on the Alimentary Tract.—Because of the intensely bitter taste of the salts of strychnine, they are taken orally in the form of the tincture or elixir as a "bitter" to stimulate the appetite and increase the flow of digestive juices. It is mainly absorbed by the intestine and after absorption it increases the movements of the bowel by its action on the muscle or ganglion plexus in the bowel wall.

Toxicology.—Cases of strychnine poisoning are fairly numerous. Strychnine is the chief constituent of most gopher and rat poisons, and as such has been a frequent source of poisoning. Cathartic pills containing strychnine are one of the most frequent sources of accidental poisoning in children. Strychnine is readily absorbed from the intestines and symptoms appear in from fifteen minutes to one hour. *Symptoms* usually are as follows: a sense of tightness in the chest, followed by a sudden tetanic spasm, characterized by stiffness of the neck, a stiff sardonic grin, extension of the legs, opisthotonus with the body resting only on the heels and head. The convulsions last from a half minute to several minutes, accompanied by cyanosis, rapid pulse, and dilated pupils. Between attacks, quiescent intervals of a few minutes follow, characterized by complete relaxation. Death occurs from exhaustion, or in the midst of a paroxysm, from asphyxia. The average *fatal dose* varies from 0.10 to 0.12 Gm., and death occurs usually after one to three hours.

Treatment.—1. Inject intravenously *immediately* 0.5 Gm. (7½ grains) of sodium amytal dissolved in 10 cc. of sterile water; *inject slowly.*

2. Repeat, as required, until the patient is in a quiet sleep.

3. If no amytal is available, substitute another barbital derivative, such as sodium phenobarbital.

4. Pass a stomach tube and wash out the stomach with a 0.1 per cent solution of potassium permanganate.

Therapeutic Uses.—Except for its use as a bitter tonic, there is no satisfactory evidence that strychnine is of material value in the treatment of disease. The preparations most frequently used are the tincture of nux vomica and strychnine sulfate. The extract of nux vomica and strychnine nitrate are used occasionally. A common error is to give too small a dose of the tincture, especially when administered by drops.

Bitter Tonic.—Strychnine is used as a bitter tonic, generally in the form of a preparation of nux vomica. It is also a tonic to the muscular system because it induces increased response to stimuli.

As a stomachic:

℞

Nux Vomica Tincture	4.00 cc. (f3j)
Compound Gentian Tincture	60.00 cc. (f3ij)
Distilled Water q.s. ad	120.00 cc. (f3iv)

M. Sig.: Two (2) teaspoonfuls in water half hour before meals.

Vision.—Strychnine has been used with some success, especially in hysteria and neurasthenic forms of amblyopia. In diminished vision, due to alcohol and tobacco, large doses often give beneficial results. It may be given internally or a 1 per cent solution may be dropped in the eye. In amblyopia, and even commencing atrophy of the optic nerve, strychnine is indicated.

Paralysis.—Strychnine and nux vomica are used to preserve muscular nutrition in paralysis associated with functional neuritis and high lesions. In such conditions administer 1 to 2 mg., three times a day. This drug may be administered in cases of *paralysis* caused by lead, in post-diphtheritic paralysis, and in paralysis due to cortical lesions. The drug is also used to raise the tone of rectal and vesical sphincters, and to improve catharsis in atonic constipation. Walshe recommends strychnine in the treatment of *beriberi*, starting with a single daily dose of 1/30 grain (0.002 Gm.) and gradually increasing the dosage.

Antidote.—Strychnine is a good antidote for the treatment of narcotic poisoning which depresses the respiratory center and spinal cord. It may be used as a stimulant in aspidium poisoning if the symptoms warrant its use. It is used in *acute* and *chronic alcoholism.*

Contraindications.—The use of strychnine is contraindicated in spasmodic and hyperirritable states, such as epilepsy, spasmodic asthma, etc.

PREPARATIONS

Nux Vomica, *Nux Vomica*, N.F., B.P. Seeds yielding not less than 1.15 per cent strychnine. *Dosage:* 0.1 Gm. (1½ grains).

Nux Vomica Extract, *Extractum Nucis Vomicae*, N.F., yields about 7.5 per cent of strychnine. *Dosage:* 15 mg. (¼ grain).

Nux Vomica Tincture, *Tinctura Nucis Vomicae*, N.F., B.P. Nux vomica (10%) yields about 0.115 per cent of strychnine. *Dosage:* 1 cc. (15 minims).

Strychnine Sulfate, *Strychninae Sulfas*, U.S.P. *Dosage:* 2 mg. (1/30 grain).

Strychnine Sulfate Tablets, *Tabellae Strychninae Sulfatis*, U.S.P. *Dosage:* 2 mg. (1/30 grain).

Brucine

Brucine (dimethoxystrychnine) and strychnine are found in equal amounts comprising about 3 to 4 per cent of the seeds of nux vomica. The drug is a bitter, white, and poisonous alkaloid. It resembles strychnine in its action but is less poisonous. Brucine is rarely used therapeutically.

DEPRESSANTS OF THE CENTRAL NERVOUS SYSTEM (NARCOTICS)

Narcosis

Drugs which depress the central nervous system also depress the cerebrum and are generally known as narcotics.

Narcosis may be defined as a temporary and reversible loss of function caused by direct action and proportional to the concentration of the drug.

Characteristics of narcosis:

1. Narcosis is characterized by a stimulation stage, e.g., ether.
2. The narcotic agents are specific for certain tissues.
3. Mechanism of action of narcotic drugs is dissimilar. Aliphatics act as general narcotics, while opium acts on specific parts of the central nervous system, mainly the basal parts of the brain.
4. The effect is physical. There is no apparent cell change.
5. Narcotic action is selective in vertebrates. It first affects the higher centers, then the lower centers. Higher concentrations affect all cells.
6. Richards (1867) found that (1) narcosis was proportional to the length of the carbon chain, (2) halogens increased narcotic action (tribromethanol is more active than ethanol), (3) hydroxyl groups decreased narcotic action (propyl alcohol is more narcotic than glycerin), (4) and that side chains decrease narcosis (iso-butyl alcohol is less powerful than butyl alcohol).

Theories of Narcosis

Several theories have been advanced in an attempt to explain the action of narcotics. Chief among the more recent theories are:

1. *The Meyer-Overton Theory.*—Meyer and Overton, working separately, pointed out that the efficiency of many anesthetic substances varied with their relative solubilities in fat and water, the more of the substance being taken up in fat, the greater the anesthetic power. The theory is based on the supposition that the character of the lipoids is changed by union with the anesthetic, thus depressing the normal functions of the nervous tissue.
2. *Theory of Moore and Roaf.*—This theory suggests that narcosis is due to a change in the protoplasm of the cerebral cells. The change consists of the formation of loose compounds of ether, chloroform, etc., with the cell proteins. This then results in the limitation of the activities of the cerebral tissues.
3. *Verworn's Theory.*—Narcosis was thought to be due to interference with oxidation of the cells. The theory advanced was that the nerve tissues, rich in lipoids, held the anesthetic substances in combination, and were thus made unresponsive to stimuli necessary for their normal metabolism. It was suggested by some that the nerve cells now were unable to utilize oxygen, and that the real basis of the anesthesia is a local anoxemia. The anoxemia theory is supported by the fact that anesthesia is produced by gases, such as nitrous oxide, which merely displace the circulating oxygen.

GENERAL ANESTHESIA

"The problem of the general nature of anesthesia is in fact unseparable from the wider problem of the nature and conditions of irritability in general."—R. S. Lillie, 1916.

Anesthesia, the art of rendering persons insensible to pain, may be considered one of the greatest advances of the past century. For centuries there have been various methods for alleviating suffering from wounds and operations, but systematic use of anesthesia dates back to 1846 when Morton and Warren demonstrated the use of anesthesia at the Massachusetts General Hospital. The choice of anes-

TABLE VIII

TABLE OF ANESTHETIC CHANGES IN INHALATION ANESTHESIA

STAGE	RESPIRATION	EYELID REFLEX	EYEBALL ACTIVITY	PUPILS		
				NO PREMED.	MORPH. ¼ GR. AND SCOP. 1/150 GR.	MORPH. ¼ GR.
First	Normal	Normal	Normal	Normal or reflex dilatation	Normal (usually)	Constriction
Second	Irregular	Normal	Active	Normal or reflex dilatation	Normal (usually)	Constriction
Third Plane I	Regular rhythm; hyperpnea; depth of respiration increased	Absent	Active	Normal	Normal	Constriction
Plane II	Same as Plane I	Absent	Paralyzed	Dilatation	Slight paralytic dilatation	Constriction
Plane III	Onset of respiratory paralysis, gasping inspiration, decreased respiratory volume	Absent	Paralyzed	Dilatation	Paralytic dilatation	Dilatation
Plane IV	Decreased respiratory volume, cessation of respiration	Absent	Paralyzed	Marked dilatation	Complete paralytic dilatation	Marked dilatation
Fourth	Paralysis of Respiration					

thetic and the technic of administration should conform to the findings of the last ten years.

In the strictest sense of the word, *anesthesia* means the absence of pain. In the more generally accepted interpretation, *general anesthesia* may be defined as a state of unconsciousness accompanied by an absence of pain and the abolition of the reflexes. Limited in this manner, we are able to distinguish between other states of unconsciousness, such as sleep, uremia, apoplexy, etc., in which the reflexes may or may not remain active and in which the unconsciousness may be partial or complete.

Analgesia is a state of partial anesthesia in which pain is absent, yet certain special senses are retained, and the reflexes usually are present to a limited degree.

Amnesia also is a state of partial anesthesia in which the cerebrum is affected predominately and forgetfulness and loss of memory are characteristic features.

Stages of Anesthesia

Inhalation anesthesia is divided into four stages (Guedel). The relative duration of these stages is the same for all agents, although the time (ether 10 to 30 minutes, chloroform 4 to 12 minutes, nitrous oxide 1 to 4 minutes, ethylene 1 to 4 minutes, cyclopropane ¼ to 3 minutes) to carry anesthesia through them varies.

First Stage (Stage of Analgesia).—This stage is characterized by loss of some pain without loss of consciousness. Mental control is progressively depressed. Pain is sufficiently reduced to allow for small operations. There is always a danger of entering the second stage (delirium) during the operation.

Second Stage (Stage of Delirium).—This stage represents the period of earliest loss of consciousness, with the higher cerebral centers abolished, leaving the secondary centers free to run wild. Physical violence and cardiac ventricular fibrillation are potential dangers. Delirium may also occur during emergence from anesthesia. Management of this stage consists in preanesthetic medication, proper restraint, avoidance of external stimuli, and a smooth rapid induction of anesthesia.

Third Stage (Stage of Surgery).—This stage may be divided into four planes. (See Table VIII.)

Fourth Stage (Stage of Respiratory Paralysis).—This stage represents the beginning of respiratory paralysis, ending in cardiac failure. The duration of the stage is short (1 to 2 minutes) in conditions characterized by high metabolic rate and a low oxygen reserve. Even though the respiration has stopped, circulation may persist and, with proper treatment, life may be restored.

Signs of Anesthesia

Respiration.—Respiration is a valuable guide in anesthesia. Premedication and operative technic have a great influence upon respiratory rate and volume during the operation. During the *first stage* respiration is normal, increasing slightly as the lower levels are reached. During the *second stage*, or stage of delirium, respiration is irregular. The depth of respiration begins to increase in the *first plane* of the *third stage*, and the rhythm becomes regular. Soon the respiratory movements become exaggerated. The respiration in the *second plane* is quite similar to that found in the first plane. The intercostal muscles gradually become paralyzed in the *third plane*. This is first evidenced

by a pause between inspiration and expiration which gradually becomes longer, while inspiration becomes shorter. The inspiration becomes gasping, accompanied by a gradual decrease in respiratory volume. The *fourth plane* is characterized by a further decrease in respiratory volume, ending finally in cessation of respiration. Paralysis of respiration marks the *fourth stage* of anesthesia.

Eyelid Reflex.—This reflex, which is tested by raising the upper eyelid with the finger, is absent in the third stage; the lid will not attempt to close.

Eyeball Activity.—The cause of this activity is unknown. The character of the movement usually remains the same. The degree of activity of the motor muscles is of value, but the type of movement is of no value. Cessation of movement marks passage of the second phase of the third stage.

Pupils.—Pupil reactions are variable. Reflex dilatation may occur in the first and second stages due to emotional excitement (especially seen in children). Reflex dilatation is absent in the third stage. Paralytic dilatation occurs in the third stage, and is due to the paralytic effect of the anesthetic or anoxia (lack of tissue oxygen). This reaction is a guide in anesthesia. Pupillary reactions (see Table VIII) are generally modified by premedication. Barbiturates have no effect on dilatation.

Swallowing, Vomiting, Etc.—As anesthesia progresses, swallowing (tested by fingers on larynx) occurs at the beginning of the first plane, immediately before vomiting. As anesthesia passes off, vomiting may then occur after swallowing. Vomiting may occur during slow induction, but it is rare during rapid induction, as the vomiting area is rapidly passed. The light reflex and the corneal reflex are of little value to the anesthetist.

Pulse Signs.—The pulse is an index of the condition of the patient. The rate, rhythm, and most important, its volume should be noted. During excitement pulse signs are of little value. When relaxation is complete the pulse signs are valuable and should be observed carefully. Either the radial or temporal arteries should be observed throughout the operation in order to recognize variations in quality.

The pulse rate will increase from pain stimuli. Certain diseases, such as exophthalmic goiter, have rapid pulse rates. A pulse rate of 140 or over is a danger signal. If the pulse rate increases and the volume becomes small, saline administration may be indicated. If the volume remains normal or constant, the progress of the anesthetic is excellent.

If the pulse stops completely, artificial respiration should be instituted at once. If the patient does not respond to artificial respiration, place him in a prone position and strike the seventh cervical vertebra severely with the wrist. This stimulation apparently tends to overcome the vagus inhibition. The hypodermic injection of atropine (1/600 gr.) has been found valuable in some cases. Massage of the heart, when the abdomen is open, may prove of benefit.

Depths of Anesthesia

Reflex response to *skin traumatism* is usually abolished by anesthesia in the upper half of the first plane. The *posterior pharyngeal reflex* is inactive below the middle of the first plane. The *cough reflex* is abolished at the junction of the first and second planes. Anesthesia at the lower border of the second plane abolishes reflex contractions of

the *abdominal muscles.* The *anal reflex* may not be abolished until the fourth plane or lower. *Vocal cord adduction,* which on expiration produces an "*expiratory grunt,*" is abolished in the lower third plane. *Intestinal peristalsis* ceases and *arterial walls* lose their tone in the lower third plane.

Operations Indicated in the Various Stages of Anesthesia

First Stage.—Since sufficient opiates cannot be administered, as they may increase delirium, obstetric procedures are indicated in the first stage.

Third Stage: *Plane I.*—Thoracoplasty (desired to retain cough reflex), thyroidectomy (little retching and vomiting desired), vaginal surgery, cystoscopy, operations on uterine cervix, operations on mediastinum (respiratory freedom desired), hernioplasty, tonsillectomy (some prefer retention of cough reflex), amputation, fractures, Cesarean section (major consideration is to prevent vomiting), etc.

Plane II.—Surgery of larynx (laryngeal reflex abolished in the upper second plane), rectal surgery (depends on nature of operation and desired sphincter flaccidity), abdominal surgery (abdominal reflexes and muscles must be relaxed), etc.

Plane III.—Internal podalic version and extraction (maximum uterine relaxation only in third plane), breech extraction (especially until breech is broken and foot brought down), etc.

Relative Potency of Various Anesthetic Agents

Nitrous oxide will carry anesthesia to the middle of the first plane; ethylene to the lower first plane; ether, chloroform, ethyl chloride, cyclopropane, divinyl ether through the third stage.

Many drugs possess narcotic, sleep-producing, and/or anesthetic properties of varying degree. However, measured on the basis of whether the drug, alone, unsupported by other drugs or preliminary medication, can produce deep and musculature relaxation suitable for any type of surgery, the number is quite low. During the course of an average general anesthesia, however, combinations of two, three or more drugs are more commonly used than a single drug.

Relative Safety of Anesthesia

The following data arranged from Trent and Gaster (Ann. Surg. 119: 954, 1944) gives information on mortality resulting from various types of anesthesia:

Anesthetic	Number of Anesthesias	Anesthetic Deaths	Number per 1,000 Anesthesias
Local	13,151	0	0
Ether	14,724	6	0.407
Nitrous oxide	6,705	2	0.295
Nitrous oxide with ether	2,175	2	0.919
Cyclopropane	5,744	4	0.691
Spinal	5,436	6	1.100
Spinal with supplement	930	2	2.150
Total	54,128	22	0.498

DRUGS COMMONLY USED FOR GENERAL ANESTHESIA

DRUG	FORMULA	VOLATILITY
1. Ether	$(C_2H_5)_2O$	36.5° C.
2. Chloroform	$CHCl_3$	61.0° C.
3. Nitrous Oxide	N_2O	- 89° C.
4. Ethylene	C_2H_4	-103° C.
5. Ethyl Chloride	C_2H_5Cl	12.5° C.
6. Cyclopropane	C_3H_6	- 34° C.
7. Avertin (Basal Anesthetic)	CBr_3CH_2OH	
8. Divinyl Ether (Vinethene)	$(C_2H_3)_2O$	28.3° C.
9. Trichloroethylene	$CHCl:CCl_2$	
10. Intravenous Anesthetics		
Thiopental Sodium (Pentothal Sodium)		
Hexabarbital Soluble (Evipal Sodium)		

The formula and the volatility of these agents are of prime importance in their electability, their adaptability, and also in their administration. Those agents with low volatility make for ease of controllability and withdrawability. Divinyl ether is more volatile than diethyl ether, hence its onset is more rapid and the recovery more quickly accomplished. Observe also that the ethyl radicle (C_2H_5) predominates in ether, ethyl chloride, and is related to the vinyl formula for divinyl ether.

Ether

Ether, ethyl oxide $(C_2H_5)_2O$, is a volatile, colorless, light liquid, with a penetrating odor. It boils at about 35° C., is denser than air, soluble in twelve parts water, and in nine parts of serum. It is a solvent for resins, fats, and oils. It is *very inflammable* and should be cautiously employed in the presence of open flame, cautery, etc. The chief impurities are acids, acetaldehydes, and peroxides. The peroxides are very irritant.

Pharmacological Action.—Ether is a general anesthetic. It possesses stimulant, sedative, anodyne, antispasmodic, carminative, diaphoretic, and anthelmintic actions.

Ether is *absorbed* at once by the lungs, and half of the ether absorbed is removed in about forty minutes by the same route. A small part is *excreted* in the urine. The rapid initial removal of the anesthetic is of great practical value, as it permits the anesthetist to vary the depth of the anesthesia rapidly. Absorption by the stomach and rectum is prompt, and this route of administration may be utilized for anesthesia.

Local Action.—Ether, being volatile, has a high vapor tension and rapidly dissolves in body fluids. It penetrates the tissues readily and causes irritation at the site of application. On evaporation it blanches and cools the skin. If applied to the skin, and not allowed to evaporate, it is more irritant and is rubefacient. Ether is very irritant to mucous membranes, therefore it must be diluted with air when inhaled.

Action on Nervous System.—After absorption ether acts mainly on the central nervous system. It has a special affinity for nervous tissues, and after death, more ether is found in the brain than in any other organ.

Ether causes a progressive depression of the central nervous system. The higher centers are first affected, then the emotions, the perceptions,

the sensory centers, the motor and cerebellar functions, the spinal reflexes, and finally the vital medullary centers.

Action on Respiration.—Breathing is quickened by reflex stimulation from the mouth, stomach, etc. After absorption therapeutic doses have little effect, but large doses depress the respiratory center, and may result in respiratory paralysis. In Fig. 1 note the depression of respiration and gradual recovery after ether is removed.

Action on the Eye.—The pupil is at first dilated reflexly, then with increased narcosis it contracts but remains sensitive to light. In deep anesthesia it is about half dilated and almost inactive to light. In collapse the pupil is dilated and insensitive to light.

Action on Circulation.—The heart is stimulated by momentary reflex stimulation of the vasoconstrictor center, and the force and arterial pressure rise. It is a slight effect and is proportional to the local irritation produced.

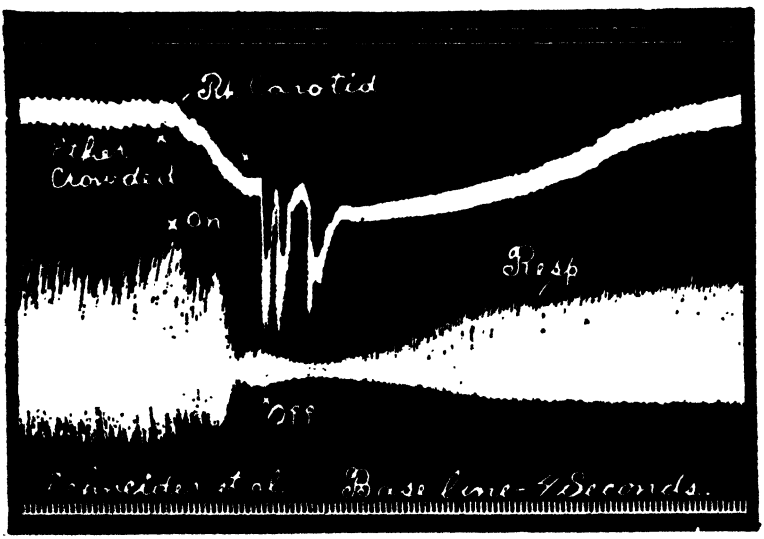


Fig. 1.—Blood pressure, respiration, base line, and time in four-second intervals showing action of concentrated ether vapor. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

The heart muscle may be temporarily stimulated, but after long anesthesia it becomes weakened. With therapeutic doses of ether there may be a rise in blood pressure for about fifteen minutes, and then a slight lowering to normal or below normal. The heart rate is somewhat increased, and there is marked flushing due to cutaneous vessel dilatation.

Action on the Blood.—Ether produces acidosis with an increased content of sugar, lactic acid, and phosphates in the blood. The coagulation time is lessened. The oxygen-carrying capacity is not reduced.

Action on the Alimentary Tract.—Ether causes a burning, unpleasant taste, irritates the mucous membranes, and causes salivation. It may cause vomiting if swallowed. If diluted it acts as a carminative and tends to expel gas and relieves the symptoms of a distended stomach pressing upon the heart. During anesthesia there is a lack of tone in the

muscles of the stomach and bowels, while on recovery they become hyperirritant.

Miscellaneous Actions.—There may be a transient impairment of *liver function* followed by hyperglycemia. The pregnant *uterus* becomes less active. Under anesthesia *kidney function* is decreased by arteriole contraction. Albumin is frequently noticed in the *urine.*

Toxicology.—Most fatal cases of ether occur during its administration as an anesthetic. Ether is a relatively safe general anesthetic, death from its use occurring less frequently than once in every 2,000 anesthesias (Trent and Gaster, 1944). Other data has shown the safety factor to be still higher (1 to 5,000 or 10,000). Sometimes it is taken orally or by inhalation for suicidal purpose. Ether is habit-forming; a few individuals swallow small amounts regularly.

The danger signals of overdosage of ether consist of pupil dilatation and changed facial expression. Usually, death is caused by respiratory paralysis with associated involvement of circulation; however, death may occur from the reflex irritation of the respiratory passages. Surgical anesthesia requires nearly a 7 per cent concentration in air, while a depressing effect is produced by a 9 per cent concentration and an 11 per cent concentration may cause respiratory paralysis. When ingested, a fluidounce may be sufficient to cause death. The *post-mortem findings* are not characteristic.

Ether has less depressant action upon the medullary centers than has chloroform. It produces a less marked fall in blood pressure and less depression of respiration than does chloroform. Delayed ether poisoning is rare, but some liver and kidney injury is produced, since acetone and diacetic acid appear in the urine after anesthesia in 50 per cent of the cases. Albumin and casts are present in 25 per cent of the cases.

Treat symptoms of ether poisoning by removing patient to fresh air, by administering artificial respiration, by injection of adrenalin (1 cc. of 1:1,000), and if indicated, by rectal infusion of saline. Administer stimulants such as caffeine.

Therapeutic Uses.—Ether is seldom prescribed as such. The spirit of ether is recommended, and is either prescribed alone or with other agents.

Surgery.—Ether is used as a general anesthetic in surgery. Locally, it is employed to cleanse the skin preliminary to surgery. For anesthesia a pure ether must be used.

Anodyne, Sedative, Etc.—Ether is occasionally administered internally, particularly in the form of the spirit, as an anodyne, carminative, sedative, and antispasmodic. It may be mixed with oil and administered by rectum (use 4 cc. of the spirit, 32.5%).

Angina Pectoris.—Ether, acting by reflex effect upon the circulation, relieves angina pectoris (use 4 cc. of the compound spirit, containing 32.5% ether, 2.5% ethereal oil).

Spasms.—Ether is administered to relieve spasms in colic, spasmodic hiccup, etc. (use 2 to 4 cc. of the compound spirit).

Ether as an Anesthetic

Ether was the first anesthetic to come into extensive use. It remains and probably will remain for many years to come our most useful anesthetic agent. It is susceptible to many adaptations and combinations and is the one reliable standard by which all other agents, methods, and results are judged.

Advantages.—It may be given by people of minimal experience with satisfactory and safe results. It may be given with little or no

expensive apparatus. Anesthesia is rapid. Complete relaxation results. The safety factor is high.

Disadvantages.—Ether is irritant to the mucous membranes and causes increased saliva and bronchial secretions. In light anesthesia this may lead to retching and vomiting. Post-anesthetic pulmonary complications are more frequent with ether. Transient albuminuria is common, indicating mild renal damage. Consequently, ether is often used with other anesthetics to limit the dose of ether necessary.

Contraindications.—Ether is contraindicated in pulmonary lesions. Even when given by rectum some ether is eliminated by the lungs and leads to exacerbation of a pre-existing disease. Diabetes is a contraindication, as the blood sugar is raised and acidosis augmented. Renal damage contraindicates ether anesthesia, as ether may injure a normal kidney.

Phases of Anesthesia.—The induction of ether anesthesia is usually unpleasant. Over-concentration of the vapor may cause coughing, respiratory spasm, and a sense of suffocation. On administration of ether there is a stage of excitement indicated by struggling and slight dilatation of the pupils. As anesthesia deepens, the pupils contract and lose their reactivity to light. The eyeballs, which have been oscillating, become fixed. At the same time breathing, which was irregular in the excitement stage, becomes deep and sonorous. In very deep surgical anesthesia, bordering on narcosis, respiration becomes shallow and irregular, the eyeballs jerk and pupils dilate. Respiration may cease.

Administration of Ether.—Ether is administered chiefly by the *inhalation* or the *insufflation* methods. It is also possible, however, to induce and maintain anesthesia by injection of ether in a suitable solution into the rectum. Another type of administration may be used for anesthetics, that is, to introduce the anesthetic into the circulation of the patient by way of the vein. Intravenous administration, however, is unsafe and rarely used.

Inhalation anesthesia consists of substituting ether vapor for the air normally used by the patient. This vapor may be administered by oral inhalation, by intrapharyngeal inhalation, or by intratracheal inhalation.

Insufflation anesthesia consists of blowing ether vapor into the patient's respiratory tract. When blown into the mouth the method is called oral insufflation; if blown into the trachea, intratracheal insufflation; if in the pharynx, intrapharyngeal insufflation.

The inhalation method is simple and requires little apparatus. It is usually the method of choice. The insufflation method requires a certain amount of complicated apparatus for best results. It is used only after induction by inhalation. It is an ideal method for surgery about the head, neck, and thorax.

A detailed discussion of the methods of administration of anesthetics would be inappropriate in a text of this size. The method of administration and the anesthetic agent must depend upon the type of operation to be performed and the age and condition of the patient. Ether may be administered as follows:

Open Drop Method.—The simplest method is to drop ether on a mask made of gauze stretched over a wire frame. It requires eight to ten minutes to obtain complete anesthesia. This method requires 90 to 120 cc. of ether per hour to maintain relaxation.

Closed Method.—For this method more elaborate apparatus is needed by which air or other gases are bubbled through ether and delivered to the patient through a tight-fitting mask. It may be given in an

ordinary gas machine after a nitrous oxide induction. It is frequently used to supplement ethylene to obtain more complete relaxation.

Insufflation.—For certain operations about the head the insufflation method is indicated. After induction in the usual way an endotracheal tube is inserted and ether vapor is delivered directly into the trachea or pharynx.

Rectal Route.—This method is efficient but depth of narcosis is difficult to control. The following formula has been suggested by McCormick for analgesia in obstetrical cases:

Ether	75.0 cc.
Quinine alkaloid	1.3 Gm.
Alcohol	3.0 cc.
Paraldehyde	8.0 cc.
Olive oil or petrolatum q.s.	120.0 cc.

PREPARATIONS

Ether, *Aether*, U.S.P., B.P.

Ethyl Oxide, *Aethylis Oxidum*, U.S.P. (Solvent ether). About 97 per cent $(C_2H_5)_2O$. Caution.—Solvent ether must not be used for anesthesia. Only ether may be used for anesthetic purposes.

Ether Spirit, *Spiritus Aetheris*, N.F., B.P. (Hoffmann's Drops), Ethyl oxide (32.5%) in alcohol. *Dosage:* 4 cc. (1 fluidrachm).

Compound Ether Spirit, *Spiritus Aetheris Compositus*, N.F. (Hoffmann's Anodyne). Ethyl oxide (32.5%), ethereal oil (2.5%), and alcohol. *Dosage:* 4 cc. (1 fluidrachm).

Chloroform

Chloroform, $CHCl_3$, is a clear, colorless, noncombustible, volatile liquid, with a pleasant odor. It may deteriorate on standing, forming free hydrochloric acid, chlorine, and carbonyl chloride ($COCl_2$). The presence of alcohol prevents decomposition. Chloroform differs widely from the other anesthetics in that it does not have the ethyl radicle in its composition and in that the molecule contains three atoms of the halogen Cl. In any combination or agent the addition of the halogens—Cl or Br—markedly increases the potency, the toxicity of that particular agent.

Chloroform was discovered by Guthrie in 1831. It was used as a general anesthetic by Simpson of Scotland in 1847, some months after the discovery of ethyl chloride by Florens.

Pharmacological Action.—Chloroform possesses general anesthetic, sedative, antispasmodic, anodyne, carminative, and rubefacient actions.

It is *absorbed* almost instantly by the lungs, and is rapidly *excreted* by the lungs. The liver plays an important part in detoxifying chloroform. Chloroform, like ether, is a general protoplasmic poison. It tends to burn the skin as it evaporates. It causes a progressive depression of the central nervous system, attacking the higher centers first. The respiratory system is greatly depressed. Chloroform is more toxic than ether to circulation, causing a fall of blood pressure (Fig. 2) due to vasomotor depression. Slight errors in administration may cause arrest of the heart due to vagus stimulation, asphyxia, fibrillation, or to direct action on the cardiac muscle. The vasoconstrictor center is slightly irritated and then depressed. Chloroform has little direct effect on blood vessels.

Toxicology.—Chloroform *is extremely toxic to young children.* As a protoplasmic poison the evil effects of chloroform may not become evident until some time after administration. These late effects are known as "delayed chloroform poisoning." The symptoms include progressive weakness, cyanosis, pallor, restlessness, vomiting, delirium, coma, and death. The organs principally affected are the liver and kidneys. The pathologic picture is that of congestion, hemorrhage, degeneration, and central necrosis. The heart muscle may be pale and show signs of fatty degeneration. Hemorrhages are particularly frequent in the serous membranes, and in the intestinal and stomach mucosae.

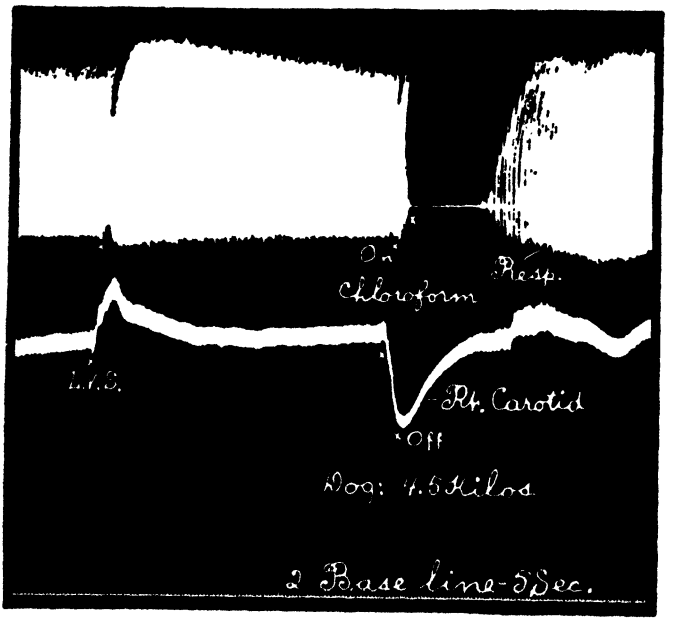


Fig. 2.—Effect of concentrated chloroform vapors on respiration (depression of the respiratory center) and on blood pressure (due mainly to depression of heart). (From Jackson: *Experimental Pharmacology and Materia Medica.*)

CAUSES OF DEATH IN CHLOROFORM ANESTHESIA.—

1. Spasm of respiration may occur during the induction stage. The spasms may allow for accumulation of chloroform which on relief of the condition discharges a lethal dose, causing death.
2. Vagus inhibition, followed by paralysis of the heart muscle, may occur in the induction stage. This is more liable to occur in nervous individuals.
3. Simple overdosage may cause death in maintenance stage.
4. Progressive acidosis may cause death during the stage of recovery.
5. "Delayed chloroform poisoning" may be followed by death.

Therapeutic Uses.—Pure chloroform is indicated for inhalation anesthesia. Chloroform water is sometimes used as a vehicle in the

administration of sedatives, carminatives, etc. Chloroform spirit may be used alone or with other agents.

General Anesthetic.—By inhalation it is used as a general anesthetic. At one time it was widely used for this purpose, but has been gradually replaced by safer agents.

Ether may be administered mixed with *chloroform* (ether 3 parts—chloroform 2 parts) or the drugs may be given alternately by the drop method. The proportion of chloroform for induction may be about 40 per cent and this is gradually decreased as the stage of maintenance is reached. The addition of ether reduces the chance of circulatory depression and improves the quality of respiration.

Counterirritant.—Chloroform acts locally as a penetrating and powerful irritant. It is an ingredient of liniments used for sprains, strains, and various other conditions.

Anodyne, Carminative, and Antihysteric.—If taken orally, small doses of chloroform are carminative and anodyne; it is therefore indicated in gastric fermentation and colic. By mouth it is used also in the treatment of acute indigestion, nausea and dysentery. For carminative, use 2 cc. of the spirit of chloroform. It is still very commonly used to produce partial anesthesia in labor when the patient is delivered in the home.

Chloroform as an Anesthetic

Chloroform is a powerful anesthetic, rapidly producing muscular relaxation with loss of reflexes. Even though potentially dangerous, chloroform is a marvelous analgesic and anesthetic agent. Chloroform is especially useful in acute respiratory conditions in small children and in analgesia in normal labor. Chloroform combines readily with ether, and synergistically with the several gaseous agents. No anesthetic agent surpasses and few approach chloroform in efficacy and potency. Some anesthetists are not in agreement with the condemnation heaped on chloroform anesthesia by the American Medical Association in 1912. Further exploration of the clinical application of chloroform should be pursued.

Indications.—Chloroform is used to replace ether when cautery is used; in alcoholics; in patients with convulsions, epilepsy, high blood pressure, and in obese persons. Patients should be placed in the Trendelenburg position.

Contraindications.—Chloroform is contraindicated in patients with diabetes, hypotension, or cardiac disease; in prolonged operations; in dental or minor surgery. It should not be administered to patients in a sitting posture, or in the presence of an open flame (phosgene).

Preparations

Chloroform, *Chloroformum*, U.S.P., B.P.

Chloroform Water, *Aqua Chloroformi*, N.F., B.P. A saturated solution of chloroform in distilled water. *Dosage:* 15 cc. (4 fluidrachms).

Chloroform Liniment, *Linimentum Chloroformi*, U.S.P., B.P. A mixture of chloroform (30%) and soap liniment and camphor.

Chloroform Spirit, *Spiritus Chloroformi*, N.F., B.P. Chloroform (6%) in alcohol. *Dosage:* 2 cc. (30 minims).

Nitrous Oxide

Nitrous oxide, "laughing gas," is a colorless gas, possessing a characteristic odor and sweetish taste. It is nonirritating to the respira-

tory tract. The boiling point of liquid nitrous oxide is -89.5° C. Its chief impurity is toxic nitric oxide. It forms an explosive mixture with ether or ethylene.

Pharmacological Action.—With nitrous oxide alone, only incomplete anesthesia can be obtained. The length of the administration is limited by its effect on the body.

Action of Nitrous Oxide.—On breathing nitrous oxide the patient experiences a sense of exhilaration, the extremities tingle and rapidly grow numb. Respiration becomes full and deep (Fig. 3). Consciousness is lost in about thirty seconds. If administration is continued, air and oxygen being excluded, the patient becomes pallid and gray. The muscles of the face are thrown into convulsions; the respiratory movements become irregular and finally cease. On administration of air normal respirations return and consciousness returns in about two minutes.

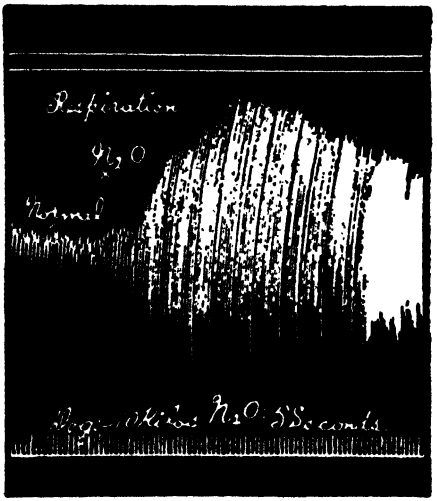


Fig. 3.—Effect of nitrous oxide on respiration. The respiration at once becomes deeper and more rapid. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

Mode of Action of Nitrous Oxide.—Nitrous oxide differs in its chemistry from all other agents. Extremely volatile, it is also extremely rapid in its effect. It is pleasant to inhale. It does not enter into chemical combination with any body tissue or fluid, entering and leaving the blood stream as such. It is strictly a sub-oxygenation anesthesia, and most unfortunately, it does not relax muscle tissue per se.

Nitrous Oxide as an Anesthetic

The anesthetic properties of nitrous oxide were known before those of ether. Its extensive use in surgery is of more recent development. It supports combustion and care must be exercised to prevent explosions of nitrous oxide and oxygen. The gas is quite inert and forms no known combination with the body cells. It apparently owes its anesthetic property to its ability to displace oxygen from

the blood stream. Nitrous oxide is readily eliminated when the pressure of nitrous oxide in the pulmonary alveoli is reduced. The factor of hasty absorption and elimination makes possible rapid induction and rapid recovery from nitrous oxide anesthesia.

Nitrous oxide finds its greatest use as a preliminary to other anesthetics which have greater effect, and in cases for which the analgesic property is wanted.

Nitrous oxide has been administered hundreds of thousands of times to a degree of partial asphyxia. Many dentists make this mistake in administering nitrous oxide. One should use shorter anesthesia, or add oxygen to the mixture.

Methods of Administration.—

1. USE OF NITROUS OXIDE TO INDUCE ETHER ANESTHESIA.—This method is common in large hospitals. The advantages are: (1) production of unconsciousness, (2) mucous membranes become less sensitive to ether vapor, and (3) production of deep breathing which permits rapid ether anesthesia.

2. USE OF NITROUS OXIDE ALONE.—This is especially indicated for the extraction of teeth, opening of abscesses, and minor surface operations. It has a valuable use in obstetrics when given with each pain of labor; when the head has reached the perineum, continuous administration is indicated.

3. USE OF NITROUS OXIDE-OXYGEN ANESTHESIA.—This method depends on a mixture of nitrous oxide and oxygen for anesthesia. For complete anesthesia, 90 per cent nitrous oxide and 10 per cent oxygen result in no asphyxia. If air (⅕ of air being oxygen) is used in place of 10 per cent oxygen the patient will show signs of asphyxia. The problem is to give nitrous oxide in sufficient concentration to produce anesthesia and still not produce asphyxia.

The signs and symptoms of nitrous oxide-oxygen anesthesia change fast. The *color* of the patient is the most reliable index of the amount of oxygen needed. Next, the *respiration* is the most valuable sign. During induction the respirations are usually more rapid and deeper than normal, while during maintenance the rhythm and depth of respiration, in conjunction with the color, form the chief guide for the anesthetist. Absolute *muscular relaxation* is impossible with nitrous oxide-oxygen anesthesia. A slow pulse, less than fifty, is a danger sign. During the maintenance stage the light reflex is active, the pupils are contracted and the palpebral and corneal reflexes are active. This anesthesia is very difficult to administer, but when administered properly it is a method par excellence.

4. USE OF NITROUS OXIDE-ETHER ANESTHESIA.—The addition of ether to nitrous oxide-oxygen increases the efficiency and the muscular relaxation. When ether is used properly with nitrous oxide-oxygen, it is an excellent and perhaps the best all-round method of anesthesia at our command. For relaxation more ether is used.

Method.—Administer a hypodermic of morphine, ⅙ grain, and atropine, 1/150 grain, one-half hour before operation.

Induction by nitrous oxide or nitrous oxide-oxygen.

For operations requiring complete muscular relaxation (intra-abdominal, gall bladder) administer ether alone.

For intestinal work stop ether and administer nitrous oxide-oxygen.

Toward the end of the operation use nitrous oxide-oxygen alone.

No after-symptoms follow this method of anesthesia administration. It produces complete relaxation, is easily controlled, and is safe.

Administration.—Nitrous oxide is given by an ordinary gas machine and a close-fitting mask. The gas valves are set so that there is approximately a 10 per cent mixture of oxygen in nitrous oxide. If cyanosis occurs, the percentage of oxygen is raised. Prolonged anesthesia is dangerous in unskilled hands because in order to produce full anesthesia it is necessary to cut down the oxygen supply to the minimum compatible with life.

Advantages.—Nitrous oxide does not irritate mucous membranes. The gas is a safe, pleasant method of anesthesia. It produces less disturbance of the vital functions than do other forms of anesthesia. In the hands of an experienced anesthetist it induces little postoperative nausea and vomiting. There is little danger of overdosage. The mortality is about one per million.

Disadvantages.—Nitrous oxide usually gives an initial increase of blood pressure and pulse rate, but otherwise has little effect upon the circulatory system. It is contraindicated for abdominal operations and for the setting of fractures because it produces an incomplete muscular relaxation. Nitrous oxide is chiefly used in adults. The disadvantage of incomplete relaxation may be overcome by the simultaneous administration of ether.

PREPARATION

Nitrous Oxide, *Oxidum Nitrosum*, U.S.P. (Nitrogenii Monoxidum, B.P.).

Ethylene

Ethylene, $CH_2{:}CH_2$, is a colorless gas which is lighter than air. The gas has a faintly disagreeable garliclike odor; in the pure state it is said to be odorless. It is inflammable and will not support combustion. With air, oxygen, or nitrous oxide, it forms explosive mixtures.

Brown and Henderson and also Luckhardt showed that ethylene was a more powerful anesthetic than nitrous oxide, and that a concentration of 90 per cent ethylene and 10 per cent oxygen usually produces sufficient relaxation for all but abdominal operations.

Trials on human subjects have demonstrated that the first plane of surgical anesthesia is easily attained and analgesia comes on readily and apparently long before surgical anesthesia is established. Administered with oxygen, it has been found more powerful than nitrous oxide and in many instances as effective as ether. However, unlike ether it causes minimal respiratory irritation and does not promote mucus secretion.

Dosage: For use the gas is passed into an inhalation apparatus and then inhaled with admixture of oxygen. The concentration employed for surgical anesthesia is never in excess of 90 per cent ethylene with 10 per cent oxygen. After induction, maintenance may often be attained with 80 per cent or less ethylene. If premedication (morphine, barbital) has been administered less ethylene and more oxygen are indicated.

Use of Ethylene and Oxygen.—When this mixture is administered the action of ethylene is rapid, the period of excitement is absent, and muscular relaxation rapidly follows. The signs and symptoms resemble those of nitrous oxide. A lower percentage of oxygen is required and fewer respiratory difficulties occur. After-effects are negligible other than an occasional nausea resulting from the odor of ethylene.

Use of Ethylene Following Nitrous Oxide-Oxygen.—Ethylene is added when nitrous oxide-oxygen is insufficient for the task. Nitrous

oxide is used for the induction; when consciousness is lost, ethylene is substituted for nitrous oxide and may be continued to the end of the operation. Nitrous oxide may be administered toward the end of the operation to wash out the ethylene.

Advantages of Ethylene.—

1. During induction there is less excitement than with nitrous oxide-oxygen.
2. Anesthesia is easily maintained.
3. There is no irritation of mucous membranes.
4. Muscular relaxation is greater than with nitrous oxide-oxygen.
5. No premedication is indicated.
6. Ethylene is very satisfactory for infants, children, and the aged.
7. There is less disturbance of vital functions than with other anesthetic drugs.
8. Little danger of overdosage.
9. Useful in thyrotoxicosis and diabetes.

Disadvantages of Ethylene.—

1. Ethylene is explosive and the commercial gas possesses a disagreeable odor.
2. It is contraindicated in upper abdominal surgery, i.e., gall-bladder and stomach operations.
3. Ethylene is not safe for operative obstetrics. Full-term babies in utero are more sensitive to this gas than are the mothers.
4. Ethylene is unsatisfactory for patients in the Trendelenburg position.
5. Bleeding is greater under ethylene anesthesia than under ether.

PREPARATION

Ethylene, *Aethylenum*, U.S.P., B.P. CAUTION: Inflammable, a mixture with air will explode.

Ethyl Chloride

Ethyl chloride, C_2H_5Cl, is a gas which boils at 12.5° C. It evaporates so rapidly that by virtue of this property it freezes the surrounding tissues and induces enough local anesthesia to serve for simple operations. The drug may also be administered by inhalation as a general anesthetic.

This anesthetic is useful in: (1) the *induction of anesthesia*, i.e., as a preliminary to ether anesthesia to destroy consciousness; (2) *incomplete anesthesia*, i.e., that type of anesthesia without the maintenance stage. This stage goes a little further than the induction stage, approaching the stage of relaxation. (3) In *local anesthesia* it may be used as a spray. See Chapter XIV.

Administration. 1. *For Induction of Anesthesia.*—Ethyl chloride may be administered by the semi-open or closed method. In the *semi-open method* the teeth are properly held apart and after the mask is adjusted ethyl chloride is carefully sprayed on the mask. Administration is continued until consciousness is lost, then ether is administered.

In the *closed method* the patient is allowed to breath naturally in a rebreathing bag. Ethyl chloride is sprayed slowly into the bag, not more than 4 cc. in all being administered.

2. *For Incomplete Anesthesia.*—The object is to produce a depth of anesthesia to the point where there is an absence of lid reflex, deep and involuntary respirations, and a decrease of excitement. Do not go to the stage of loss of corneal reflex and a dilated pupil.

The toxic actions of ethyl chloride consist of a depressing effect on the central nervous system, a derangement of the conduction of the cardiac muscle, and the production of myocardial weakness. When ethyl chloride is administered, consciousness is rapidly lost. In overdosage it is as fatal as chloroform. Masseteric spasms may often follow its use; therefore, a cork should be placed between the patient's teeth before administration. Embly found that it produces a less toxic action upon the heart than chloroform. Its administration is often followed immediately, or delayed for five or six hours, by headache, nausea, and vomiting. Connell says that severe headache, nausea and vomiting, severe prostration and "a delayed collapse have added a number of fatalities to the score of this anesthetic."

Ethyl chloride is frequently used in place of nitrous oxide but such a use is unjustifiable. T. D. Luke says, "The idea has gotten about among a large number of both the medical and dental profession that ethyl chloride is sort of a glorified nitrous oxide, which one may carry about in one's waistcoat pocket and administer to all and sundry, without any special precaution or skill on the part of the administrator. . . . Nothing further from the facts could be imagined. . . . Its highly toxic character and the danger due to the great rapidity of its action should be fully recognized as well as its admirable properties as an adjuvant to chloroform and ether."

Indications.—Ethyl chloride acts well in anesthetizing children. It may be used for short operations, such as the removal of tonsils and adenoids, dental cases, and as an introduction to ether. It is contraindicated in long operations and in operations in which complete relaxation is required. The anesthetist should anticipate the dangers of this drug: mainly, asphyxiation due to spasm of the respiratory tract, and secondly, overdosage.

Preparation

Ethyl Chloride, *Aethylis Chloridum*, U.S.P., B.P.—C_2H_5Cl.

Cyclopropane

Cyclopropane, a recently introduced gaseous general anesthetic, is an isomer of propylene and possesses the following formula  . It is explosive in anesthetic concentration of less than 15 per cent, hence it presents a greater fire hazard than ethylene. It is heavier than air, 1.46, and thus tends to flow to the floor. The gas in high concentrations readily diffuses through and destroys rubber.

The gas was first proposed by Henderson and Lucas (1929) as a promising anesthetic. The clinical use was well established by Waters and Schmidt (1934), and Bourne (1934).

Cyclopropane as an Anesthetic

Cyclopropane has more or less replaced ethylene as an anesthetic because of smoother induction and greater muscular relaxation. Moreover, it can be combined with a high percentage of oxygen and still maintain adequate anesthesia. It should be administered with great caution. During induction careful attention should be paid to the pulse and respiration. Any sign of arrhythmia or change in respiration is a danger signal of great importance. Muscular relaxation is much better than with nitrous oxide, although not as complete as with ether.

Cyclopropane differs from other gaseous anesthetic agents in that a low percentage of anesthetic agent (cyclopropane, 15 to 40%) is used with a high percentage of oxygen (60 to 85%). The high percentage of oxygen is an advantage. There is evidence to indicate that the cyclopropane diffuses about twice as fast as ethylene. It is eliminated less rapidly than ethylene but much faster than ether. Thus induction and recovery with cyclopropane are slower than with ethylene but more rapid than with ether.

Cyclopropane is said to affect the autonomic nervous system to a greater degree than ether or chloroform. In high concentrations it raises the irritability of the heart and predisposes to the occurrence of cardiac arrhythmias. This effect is accentuated by the simultaneous use of epinephrine and related compounds. Cyclopropane does not stimulate respiration, hence preoperative sedation with respiratory depressants must be employed with caution. The signs of Guedel (see Table VIII) for other anesthetic agents do not apply to cyclopropane, so familiarity with the particular signs and symptoms of cyclopropane is essential.

Cyclopropane is indicated for use as a general anesthetic for all kinds of operations. It has been recommended especially in obstetrics. It should be administered only by a trained anesthetist.

Administration.—Owing to the cost of cyclopropane, its administration must be carried out with carbon dioxide absorption technic to save the gas. A scale for volume mensuration of both oxygen and cyclopropane is essential.

Dosage.—In use the gas is passed into an inhalation apparatus of the closed circuit type and is then administered by inhalation from a rebreathing bag, usually with the admixture of oxygen. The concentration employed varies from 15 to 40 per cent. However, the concentration probably should not exceed 30 per cent. The remainder of the mixture should consist of a minimum of 20 per cent oxygen. Less cyclopropane is required when other anesthetics are used in combination or when premedication has been employed.

Premedication is not necessary. Some advise the use of one-half dose of morphine and an ordinary dose of hyoscine; others prefer the use of avertin. *Induction* is attained by the use of from 13 to 23 per cent. There is salivation if the gas is pushed, and stridor may develop. Due to the high percentage of oxygen used, cyanosis does not appear as a consequence of depressed respiration.

Maintenance is attained at from 7.5 to 13 per cent concentration. During the maintenance stage respiration is quiet and shallow. The deep reflexes are active. Slowing of the pulse below sixty is a danger signal of utmost importance. An irregular or rapid rhythm is an indication to stop the gas. The signs of anesthesia are valuable guides and should be observed closely. Recovery is rather slow, taking usually from one to three minutes.

Its outstanding *advantage* is that it is nonirritant and, owing to the low concentration at which it need be used, asphyxia does not arise. There are less postoperative nausea and pulmonary complications following its use.

The *disadvantages* of the compound are that it is explosive, it depresses respiration, there is difficulty in detection of planes of anesthesia, it has a tendency to produce cardiac arrhythmias, and, like ether, it causes a rise in blood pressure. There is an occasional danger of atelectasis through reduced pulmonary ventilation. High concentrations may cause lung collapse in prolonged laryngeal spasm. Postoperative excitement is occasionally experienced following its use.

With regard to its use as an anesthetic, Dr. L. F. Siese (1937) says "... while it has certain disadvantages, and considerably more investigation, particularly of its effect on the circulatory system, is needed, it more nearly approaches the ideal inhalation anesthetic than any other drug which is available at the present time."

Preparation

Cyclopropane, *Cyclopropanum*, U.S.P.

Caution.—Cyclopropane is inflammable and its mixture with oxygen in air will explode when brought in contact with a flame or an electric spark.

Tribromoethanol (Avertin)

Tribromoethanol, or avertin (CBr_3CH_2OH), has become popular as a basal anesthetic. Its usefulness, however, should not be pushed beyond the needs for basal anesthesia only. It was introduced in 1928 as a general anesthetic but now is considered as probably the best of our basal anesthetics. Many fatalities attended its use as a general anesthetic.

Tribromoethanol is a white solid, soluble with difficulty in water (3% at 40° C.). Heating may cause it to break down to an irritant dibromacetylaldehyde which causes violent rectal irritation. In order to avoid this danger avertin is supplied in solution in amylene hydrate, and this "avertin fluid" readily dissolves in water; 1 cc. of avertin fluid contains 1 gram of avertin.

With rectal injection of tribromoethanol, 50 per cent may be *absorbed* in ten minutes, 75 per cent in twenty-five minutes, and the remainder slowly (Speigel, 1930). Absorption is said to be valuable and the quicker the drug is absorbed the greater is its narcotic action. For this reason a correct technic of administration is necessary.

Tribromoethanol is detoxified in the liver when it is combined with glycuronic acid to form urobromic acid, which is rapidly excreted by the kidneys. Seventy to eighty per cent is said to be excreted in the urine in thirty minutes. The drug may injure the liver and kidneys and, in general, the toxic effects resemble the effects produced by chloroform.

Tribromoethanol as an Anesthetic

Tribromoethanol is rapidly absorbed from the rectum and produces narcosis in fifteen minutes. Approximately 50 to 60 mg. per Kg. body weight produces drowsiness, amnesia, and sleep. Seventy to 80 mg. per Kg. body weight produces unconsciousness and analgesia. The condition resembles normal sleep of several hours' duration. The pulse is slow and respiration becomes deeper and slower. Muscular relaxation is very good. The patient should be watched to prevent swallowing his tongue. Avertin, in safe dosage, produces incomplete analgesia and should be supplemented by procaine, ether, or nitrous oxide.

Toxic doses produce severe respiratory and circulatory depression with cyanosis. Carbon dioxide and oxygen are indicated to stimulate respiration, and strychnine or picrotoxin, to counteract medullary depression. Ephedrine, caffeine, and oxygen therapy are said to be effective antidotes against respiratory and surgical depression.

Administration and Dosage.—Avertin is indicated as a basal anesthetic. Avertin with amylene hydrate is said to be useful in the control of certain convulsions, such as tetanus. The *contraindications* include liver and kidney disease, severe cardiac disease, old age, shock or de-

hydration, sepsis, toxemias, pulmonary disease, marked hypothyroidism, obesity, asthenia, ileus, enteritis, and acidosis.

Avertin with amylene hydrate is administered rectally in 2.5 per cent solution in warm distilled water (40° C.). The ordinary maximum dose for basal anesthesia is 80 mg. of avertin (40 mg. of amylene hydrate) per Kg. of body weight. Often less drug is sufficient. The drug is usually stated in milligrams of avertin component although amylene hydrate adds materially to the narcotic effect. The total amount administered should not exceed from 6 to 8 cc. of avertin with amylene hydrate for women, or from 9 to 10 cc. for men. Avertin has a narrow index of safety and should be used with caution in selected cases and not as a routine (Flagg, 1939).

PREPARATIONS

Tribromoethanol, *Tribromoaethanol,* U.S.P. *Dosage:* Rectal (for each Kg. of body weight) 60 mg. (1 grain).

Tribromoethanol Solution, *Liquor Tribromoaethanolis,* Solution of tribromoethanol in amylene hydrate, U.S.P. *Dosage:* Rectal, for each Kg. of body weight, 0.06 cc. (1 minim).

Vinyl Ether (Divinyl Oxide)

Vinyl ether, divinyl oxide, CH_2:CHOCH:CH_2, is a clear, colorless, volatile liquid, with an odor like that of gasoline. It is more readily volatile than ether, and is equally inflammable and explosive. Since it decomposes in light it must be kept in a dark place. The low boiling point (28-31° C.) favors its quick action and rapid recovery. Vinyl ether has a wide margin of safety. A very low concentration is necessary for anesthesia, thus greater care in its administration must be taken to prevent overdosage.

With vinyl ether it is easy to pass from the level of surgical anesthesia to dangerous overdosage, therefore close observation on the part of the anesthetist cannot be overemphasized. Continuous administration is indicated during maintenance. Recovery is rapid following withdrawal of the drug and the patient is completely oriented and ambulant within a few minutes. It is important to remember that the eye signs are unreliable with vinyl ether. The most important guide is the rate, depth, regularity, and smoothness of respiration. Cyanosis should not occur; if present, administer oxygen, and substitution of another anesthethic is indicated. Nausea and vomiting occur in about 5 per cent of the cases. Other postoperative complications are rare.

Administration.—Vinyl ether is useful primarily in minor surgical operations of short duration, and in dentistry where gas anesthesia is not available. It has been used quite extensively during labor and during postpartum obstetric procedures. Overdosage may cause inhibition of respiration associated with anoxemia and cyanosis. Stimulate respiration and provide an adequate airway between the lungs and the atmosphere. Its use is usually contraindicated in cardiovascular disease, renal insufficiency, and hepatic damage.

Vinyl ether may be administered by the open drop, semi-open drop, or closed machine method. The open drop method is the choice for short operations. An adequate oxygen or air supply is essential and an unobstructed airway should always be maintained.

PREPARATION

Vinyl Ether, **Aether Vinylicus,** U.S.P. (Divinyl Oxide). Contains about 96 per cent vinyl ether and about 4 per cent alcohol (dehydrated). It may contain 0.025 per cent of harmless preservative.

Trichloroethylene

Trichloroethylene is a sweet-smelling, pungent, colorless, volatile liquid, having the formula $CHCl:CCl_2$. It is not inflammable; it is slowly decomposed by light, is practically insoluble, and is miscible with ether, alcohol, and chloroform; it dissolves most fixed and volatile oils.

Mode of Action.—The drug is effective only against the trigeminal type of neuralgia, and to some extent the glossopharyngeal type. The mechanism of action is unknown. The effect may be due to impurities in the anesthetic, but it is more likely that the relief obtained is due to the central depressant action of the drug. The permanency of relief reported by some persons is difficult to explain.

Toxicology.—Although no serious consequences are likely to follow its use, there is danger of overdosage from self-medication. Severe toxic psychoses have been reported. Lassitude, nausea, giddiness, and palpitation have been occasionally observed. Addiction to trichloroethylene may occur.

Therapeutic Uses.—Trichloroethylene is useful in *trigeminal neuralgia* for relief of severe paroxysms of pain. It has also been proposed for the treatment of attacks of *angina pectoris. Administration and Dosage:* Trichloroethylene is a general anesthetic subject to all the dangers and disadvantages of anesthetics. Administer 1 cc. by inhalation, repeat after a few minutes if necessary. It sems probable that not more than sixty minims should be inhaled within twenty-four hours when it is used for any considerable period of time. This drug should always be administered with the patient in a reclining position, and the drug should not be substituted for amyl nitrite or nitroglycerin in the treatment of attacks of angina pectoris. Excessive dosage of this drug may mask signs of coronary pains indicative of overexertion of the heart.

Preparation

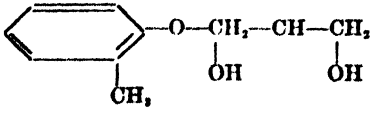
Trichloroethylene, *Trichloroaethylenum,* U.S.P. *Dosage:* Inhalation, 1 cc. (15 minims).

Curare

Sir Walter Raleigh brought the arrow poison, curare of the Aroras from "the large and beautiful land of Guiana" in the sixteenth century, but it was not until 1865 that Claude Bernard showed that its principal action was the paralysis of transmission at the neuromuscular junction. Clinical interest in curare was renewed after Bremer in 1927 discovered that small doses, insufficient to paralyze the intact skeletal musculature or to embarrass respiration, selectively released the spasm of decerebrate rigidity.

The preparations obtained were crude, brown masses with a variable potency. With the advent in 1938 of a purified and standardized preparation known as intocostrin, clinical trials in various convulsive and spastic conditions were feasible. The curare preparations available include intocostrin (20 units per cc.) and d-tubocurarine chloride, 3 mg. per cc. The activity of 20 units of intocostin is equal to that of 3 mg. of d-tubocurarine.

Recently, a synthetic preparation, α, β, dihydroxy (2-methyl), phenoxypropane (myanesin or B.D.H. 312), with curare-like effect has



been used in Great Britain. It appears to exert its muscular-relaxing action by a depressant action on the excitability of the spinal cord. It is much less toxic than curare, there is no intercostal paralysis with average therapeutic doses.

Pharmacological Action.—The chief action of curare is the arrest of all voluntary movements by an interruption of the connection between the peripheral nerves and the striated muscle fibers. When a solution of curare is given hypodermically, it causes paralysis of one muscle after another, until total paralysis results. Eventually the respiration ceases and asphyxia follows; this condition, however, is not followed by convulsions, as the motor impulses are unable to reach the muscles. Large doses cause heart failure from asphyxia and not through direct cardiac action.

The action of the drug is brief because of rapid *excretion* and *destruction*. If respiration is embarrassed or arrested, neostigmine, a physiologic antidote, will assist in counteracting the curare effect. Artificial respiration is also indicated.

Absorption and Excretion.—Curare is excreted apparently unchanged by the kidneys, but if given orally, some of the drug is detoxified in the liver and intestines. The drug may be swallowed with no ill effects, provided there is no wounded surface in the course of the digestive tract. This is explained by the fact that excretion is apparently as rapid as absorption, so that its accumulation is insufficient to affect the tissues. The inactivity of the drug, when administered orally, is also explained by some, as being due to its destruction by the liver. Others believe that the drug is rendered inactive by its passage through the stomach membranes.

Site of Action.—On stimulation of an isolated nerve of a muscle-nerve preparation, contraction of the muscle follows. When, however, the muscle is immersed in curare solution no effect results on stimulation of the nerve, but contraction follows direct muscle stimulation. This demonstrates that the paralysis is peripheral, and that the curare action is on the connection between the nerve and the muscle.

It has been partially accepted that the site of action of curare is on the motor end plates. Langley has shown that curare continues to act after the muscle plate has lost its function. He showed that the action of nicotine on the muscle plate is opposed by curare, both in normal muscles and in muscles in which the nerve and nerve endings are degenerated. The action of curare might, therefore, be said to be exerted not on the end plate, but on some substance that serves to transfer the nerve impulses from nerve end plate to the contractile substance of the muscle.

Therapeutic Uses.—Carefully standardized preparations are used to mitigate the convulsions of the shock treatment of mental cases; and to secure muscular relaxation in surgical anesthesia, especially by cyclopropane, thiopental, and nitrous oxide since it induces muscular relaxation without the use of high concentration of the anesthetic.

Curare in Anesthesia.—Administer intravenously from 40 to 100 units of intocostrin or 6 to 15 mg. of d-tubocurarine chloride when the patient is in light surgical anesthesia. Muscular relaxation occurs in from one to two minutes and persists for from fifteen to thirty minutes. If ether is used as the anesthetic agent, reduce dosage of curare preparation by 30 per cent or more, since ether has a curare-like action itself. *Remember* the usual signs in judging the depth of anesthesia may be abolished by curare preparations.

Curare may be of value to relieve spasticity in *tetanus, encephalitis,* and *poliomyelitis.* Cullen and Quinn (1943) reported that intocostrin, either intravenously or intramuscularly, was spectacular in relieving the symptoms of *tetanus. Dosage:* 8 to 10 mg. per Kg. was satisfactory.

Weed, Purvis, and Warnke (1948) reported relief of *tetanic muscle spasms.* They used d-tubocurarine, intramuscularly—3.5 to 4.0 standard units of d-tubocurarine per kilogram of body weight as the initial dose. The daily maintenance dosage varied from 1.25 cc. for a 35 Kg. boy to 2.0 cc. for an 80 Kg. man. The relaxant effect was apparent within one to three hours after injection. They administered total doses of d-tubocurarine ranging from 2,485 standard units in eleven days to 3,570 standard units in fourteen days. Each cubic centimeter of the preparation used contained 27 mg. d-tubocurarine chloride pentahydrate (equivalent to approximately 175 units) and 48 mg. of myricin (wax) suspended in peanut oil.

Early reports indicated that curare may give relief of spasticity in poliomyelitis (Ransohoff, 1945). More recent reports from the Mayo Clinic (1947), however, were not as promising. Recently, curare has been tried (Schlesinger, 1946) and might have some value in rheumatoid arthritis.

Myasthenia Gravis.—Curare has been used as a diagnostic aid in patients suspected of having this condition.

Oxygen

Although Beddard and Pembrey (1908) observed that inhalation of oxygen results in decreased pulmonary ventilation in cases of cardiac failure, the origin of modern oxygen therapy may well be attributed to Haldane, through his work on the treatment of gassed soldiers during World War I.

Physiology of Oxygen Therapy.—Under normal conditions an individual requires for maintenance of bodily health from 15 to 18 cc. of oxygen per breath. Only 21 per cent of the inspired air is oxygen, and since the tidal air is approximately 500 cc., this means that only about one-fifth of the available oxygen is used. Although this seems to be a generous reserve, in diseased states, especially those accompanied by fever, the oxygen requirement rapidly rises. The rise in oxygen requirement plus the reduction of vital capacity occasioned by consolidation and edema soon cut down on this reserve. An increased pulse rate plus an increased capacity of the blood to carry oxygen help to supply oxygen but gradually oxygen unsaturation increases. The available oxygen in the inspired air remains the same. Although respirations become more rapid, they also become shallower at the same time. Hence a vicious circle is set up which can only be counteracted by increasing the oxygen concentration of the inspired air. This can be accomplished by administering oxygen in higher concentrations than are found normally in the air.

Anoxemia.—The primary indication for oxygen therapy is anoxemia, a condition characterized by a deficiency in the oxygen content of blood. The body cells utilize oxygen brought to them by the hemoglobin for the processes of metabolism. The cells must receive oxygen in proper quantities and also at sufficiently high pressure. In anoxemia the body cells receive oxygen from the blood at an abnormally diminished pressure. In mountain sickness, a simple form of anoxemia, the pressure of oxygen in the air is reduced. At an altitude of 10,000 feet it is 116 mm. At sea level the partial pressure of oxygen in air is about

160 mm. This condition usually causes symptoms of headache, vertigo, epistaxis, nausea, vomiting, cyanosis, and dyspnea. Anoxemia is best treated by oxygen administration.

Therapeutic Uses.—In ordinary clinical practice oxygen therapy is used in preventing postoperative pneumonia in pulmonary edema, in pneumonia, and in heart disease. It is also indicated in the treatment of carbon monoxide poisoning, lung collapse, asthma, and other conditions of a similar nature. A mixture of oxygen and 5 to 7 per cent carbon dioxide is used in resuscitation.

Oxygen should be given continuously if indicated. It is good practice not to wait until there is marked cyanosis before administering oxygen. The oxygen gradient should be increased before the mechanism that prevents cyanosis is exhausted.

In Anesthesia.—Oxygen is an important constituent of various anesthetic gas mixtures. It is indicated for relief of asphyxia and difficult respiration.

Migraine.—Oxygen is useful in the abortion or termination of migraine. Alvarez reported that 88 per cent of ninety-seven cases with "typical migraine" headaches were relieved. Oxygen may be of benefit when ergotamine fails.

Shock.—Inhalation of high concentrations of oxygen is beneficial in shock. It should be employed in addition to other standard therapeutic procedures.

Heart Disease.—Oxygen is often used in the treatment of decompensated heart disease, a condition characterized by a so-called "stagnant anoxemia" in which the minute flow of blood is diminished. Oxygen therapy relieves the symptoms of dyspnea, cough, and slow pulse rate.

Lung Collapse.—Artificial Pneumothorax: Oxygen or oxygen and air, or air and nitrogen may be injected into the pleural cavity when lung collapse is indicated. If only temporary compression is desirable, air, or a gas rich in oxygen, seems indicated, as its absorption is more rapid. Nitrogen is indicated in prolonged compression, as it is less readily absorbed.

Cardiac Asthma.—Oxygen is indicated to promote oxygenation of blood in the available alveoli. In the lungs an atmosphere rich in oxygen should be supplied. A catheter is inserted in one nostril until the tip lies at the level of the uvula. Administer oxygen at the rate of six to eight liters per minute.

TECHNIC OF OXYGEN THERAPY.—The technic of oxygen therapy is not simple. To be effective, a mixture of air containing from 40 to 60 per cent oxygen, is indicated. Oxygen may be administered by inhalation through a nasal catheter, by a well-ventilated oxygen tent, and by the oxygen chamber method.

Nasal Catheter Method.—The administration of oxygen from small tanks with a funnel is not satisfactory. The funnel must be held close to the face, which interferes with the escape of carbon dioxide and moisture, or at such a distance as prevents an adequate increase of concentration of oxygen in the air breathed. An excellent method is the use of an inhaler which delivers the moistened oxygen just inside the nares, or with a catheter leading to the nasopharynx. A concentration of 35 per cent may be obtained by means of a size 10 or 12 nasal catheter, with a calibrated gauge to fit a high pressure tank. At the rate of 4 to 5 liters per minute pass through about three inches of water to prevent drying of the mucous membrane. Insert to the base of the uvula (4 inches) and change to other nostril every twelve hours.

Oxygen Tent.—When higher concentrations of oxygen are desired or when the patient has difficulty breathing through the nose, the oxygen tent can be profitably employed. The oxygen concentration is from 40 to 50 per cent. Only tents which are properly ventilated and cooled should be used.

Oxygen Chamber.—This is a very efficient and comfortable method of administering oxygen. The atmosphere is maintained at from 40 to 50 per cent oxygen.

PREPARATION

Oxygen, *Oxygenium*, U.S.P.

Oxygen-Carbon Dioxide Mixtures

The use of carbon dioxide therapy has been the source of considerable controversy during the last twelve years.

Pharmacological Action.—It has been shown that decreased carbon dioxide content of the blood is due to the increased breathing which oxygen want has promoted. Haldane and his associates (1935) showed that the volume of breathing of normal individuals was controlled in part by the concentration of oxygen in alveolar air. An increase in the carbon dioxide in the alveoli increased the breathing in proportion to the carbon dioxide present; oxygen want stimulates breathing by heightening the sensitivity of the respiratory center to carbon dioxide.

Henderson and Haggard (1920) developed the theory that loss of carbon dioxide from the blood was a serious condition which should be cared for by inhaling oxygen containing 5 to 10 per cent carbon dioxide. They considered that oxygen want was the first stage of asphyxia; the second stage followed, due to increased breathing which lowered the carbon dioxide content of the blood; and finally the third stage which is characterized by a compensatory decrease in bicarbonates. It was shown that by administration of carbon dioxide in concentrations from 5 to 10 per cent with oxygen increased the bicarbonate content of blood.

The inhalation of carbon dioxide has other physiological effects which are significant, such as increased pulmonary ventilation and increased muscle tonus (Henderson, 1938). Following operations the anesthetic gases are more rapidly eliminated from the lungs. In respiratory depression oxygen-carbon dioxide mixtures stimulate the respiratory center and tend to overcome anoxemia more quickly than with the use of oxygen alone.

Therapeutic Uses.—The most significant uses for oxygen and carbon dioxide mixtures appear to be in the treatment of *respiratory depression* in such conditions as carbon monoxide poisoning, drowning, electric shock, morphine and alcohol intoxication. The most generally recommended mixture is 5 or 7 per cent carbon dioxide with oxygen. In respiratory failure in newborn infants, the inhalation of oxygen-carbon dioxide mixture has been recommended by Henderson (1934). Some, however, advise against its use. Kane and Kreiselman (1930) express their views in the following words: "The use of carbon dioxide as a resuscitating agent in asphyxia neonatorum is not only superfluous but may be even harmful in that it tends to aggravate an already existing acidosis."

In general, it seems apparent that the marked benefit from administering a combination of oxygen and carbon dioxide arises from a heightened pulmonary ventilation, an increased muscle tonus, and

from stimulation of the respiratory center. These effects result in a more rapid disappearance of the anoxic state.

Usually the indication for use of oxygen-carbon dioxide mixtures is in cases that require a maintained increase in pulmonary ventilation; if this can be secured by relatively low concentrations, higher concentrations should not be used.

Contraindications.—In any state in which pulmonary edema is suspected, concentrations of from 5 to 10 per cent carbon dioxide are definitely contraindicated (Boothby, 1932). In congestive heart failure, pulmonary emphysema and fibrosis, concentrations of 5 to 10 per cent, administered for from five to ten minutes, may produce a shortness of breath. In massive collapse of the lungs the inhalation of carbon dioxide should only be persisted in until the breathing has been markedly increased in depth, usually a period of about five minutes.

Administration.—The simplest method of administering oxygen and carbon dioxide is to use a cylinder containing the mixture desired. These mixtures may be administered with a nasal catheter, but higher concentrations of carbon dioxide or larger flows of carbon dioxide and oxygen mixtures have to be used because during inhalation the mixture is diluted considerably. Carbon dioxide may also be administered in an oxygen tent; here again higher concentrations of carbon dioxide than 5 to 10 per cent or larger flows of the mixture are indicated in order to obtain the carbon dioxide concentration desired.

In resuscitation cases, the 7 per cent carbon dioxide and 93 per cent oxygen mixture may be administered through a mask during inhalation and exhaled through an expiratory valve during expiration. The mixture is best delivered from the cylinder into a bag and then to the mask. The rate of flow is regulated by the gauge.

INTRAVENOUS ANESTHESIA

Intravenous anesthesia is confined almost exclusively to the use of thiopental sodium (pentothal). Hexobarbital soluble (evipal sodium) is used to a much lesser extent. The latter, because of its toxicity, has been replaced by thiopental sodium. A few other short-acting barbiturates have been developed but at present have not come into general use.

Intravenous anesthesia is that type of anesthesia in which we introduce the anesthetic agent into the venous circulation of the patient. The idea of intravenous anesthesia has intrigued medical men for many years. The first attempts at this type of administration were made in 1872. Various drugs have been used, such as chloral hydrate, hedonal, sodium amytal, sodium nembutal, and ether; but the results have been generally unsatisfactory.

Recently, with the introduction of the truly short-acting drugs, such as hexobarbital sodium and thiopental sodium, satisfactory anesthesia has been attained.

Recent Trends.—(1) The original technique of giving large doses of the anesthetic agent and withdrawing the needle has been abandoned in favor of intermittent injections of doses that are safe but sufficient.

(2) The use of 2.5 per cent solutions in place of 5 or 10 per cent solutions prevents untoward results from extravenous injections.

(3) The use of intravenous anesthesia as a part of a balanced anesthesia has been the latest trend. Thus preliminary medication with

sodium pentobarbital, together with morphine sulfate and atropine, is given. Then local, regional, or spinal anesthesia is employed together with intravenous anesthesia with pentothal sodium at the same time that a mixture of 50 per cent nitrous oxide and 50 per cent oxygen is administered by inhalation.

(4) The intravenous method is still in the early stage of development. The method will be used more and more with the advent of better agents and as experience in its use is attained.

The advantages of intravenous anesthesia are:

1. Induction is rapid, within a few seconds, if so desired.
2. Induction is smooth, easy, and pleasant for the patient.
3. The postoperative condition of the patient is usually excellent, and there is a minimum of nausea and vomiting.
4. Complications are rare.
5. There is no fire or explosion hazard.

The disadvantages of intravenous anesthesia are:

1. Difficulty in making injection in obese individuals and in children.
2. Possibility of venous thrombosis.
3. Possibility of cerebral anemia in patients in sitting position if interval is longer than five to eight minutes.
4. Control of anesthesia not as sure as with inhalant anesthetic agents.

Thiopental Sodium

Thiopental sodium (pentothal) is a sulfur-substituted pentobarbital sodium compound, qualitatively similar in action to pentobarbital, but of shorter duration and effective in smaller doses.

It is rapidly destroyed in the body and if administered slowly, fairly satisfactory control can be secured. It is believed to be destroyed in the liver.

Therapeutic Uses.—The principal use of thiopental is for intravenous anesthesia. It is injected in freshly prepared buffered solutions as a quick-acting general anesthetic for short operations.

The blood pressure usually falls immediately after injection of the drug but soon returns to normal. The pulse is slightly increased. Respiration is little affected under therapeutic conditions. The main toxic effect is on respiration, since the heart is still beating effectively when respiration is paralyzed. There is little effect on blood chemistry or renal function, though the blood sugar is slightly raised.

Thiopental should be used with extreme caution in patients who have had recent severe hemorrhage or who are suffering from shock or toxemia. It is recommended that concentrations of 2.5 per cent, or less, be used, as more concentrated solutions have a greater tendency to cause venous thrombosis.

Administration.—*Premedication* is very essential to obtain perfect relaxation and should consist of an opiate and atropine sulfate. The preliminary administration should be given thirty minutes before starting the anesthetic. Atropine sulfate should be given in all cases to prevent laryngeal spasm. The opiate may well be omitted in obstetrical cases.

There is no single method of induction, the details of which all agree are perfectly satisfactory. It is necessary to remember that these drugs are potentially dangerous and should be administered only by competent, experienced anesthetists.

When the preparation of the patient is complete and the surgeon is ready, the anesthetist fixes 20 cc. of a 5 per cent thiopental sodium

solution in a 20 cc. syringe. The antecubital fossa of the arm is cleaned with alcohol, then, with a 20 gauge needle on the syringe, the median basilic vein (or a dorsal metacarpal vein in the back of the hand) is pierced. Then the anesthetist tells the patient to count aloud while the injection is made.

Dosage.—Two or 3 cc. of a 5 per cent solution (from 0.1 to 0.15 Gm.) are injected in about ten or fifteen seconds. When the patient stops counting, the injection is then stopped to permit the complete effect to appear, which requires from 30 to 35 seconds. If relaxation has not occurred, an additional 2 or 3 cc. may be injected at the same rate as before.

Following injection the respiration usually becomes quite shallow, amounting practically to apnea, but the pulse remains full and strong, and respiration soon returns. The patient should be watched closely for respiratory obstruction since, as the muscles relax, the tongue is apt to fall back in the throat and produce obstruction. It is well, therefore, at the start to have the patient's head turned to one side and to have an airway ready for immediate use.

During the period of anesthesia, the needle is allowed to remain in the vein and injection is resumed as indications warrant, 1 cc. being administered intermittently throughout the operation to maintain anesthesia at the desired level, the dose being regulated entirely by the effect produced. Evidences of recovery, which are an indication for an additional ½ to 2 cc., if the anesthesia is to be prolonged, are slight movements of the fingers and toes, or slight phonation. There are no dependable eye signs and the anesthetist will find respiration, pulse, and response to skin pinch valuable signs. The reaction to pinch of the skin has been one of the most reliable guides to depth of anesthesia.

Oxygen should be administered if the patient becomes anoxemic. Carraway (1939) recommends the use of oxygen. He writes: "Before we started using nasal oxygen, often there were complications during the anesthetic, such as hiccoughing, a slight pallor, depression of respiration and in a few instances cyanosis. Certain stimulants, such as coramine, picrotoxin, amyl nitrite and oxygen with 5 per cent carbon dioxide were given; but since we have been using nasal oxygen, none of these complications have occurred." Dr. Carraway's statement has been based on the use of thiopental sodium in 3,559 consecutive cases.

PREPARATIONS

Thiopental Sodium, *Thiopentalum Sodicum*, U.S.P. (Thiopentane Soluble). Contains not less than 89 per cent of thiopental. *Dosage:* 2 to 3 cc. of a 5 per cent solution of the sterilized drug is injected intravenously over a period of ten to fifteen seconds, and a period of thirty to thirty-five seconds is allowed to elapse before administering additional amounts that may be needed to produce relaxation.

Sterile Thiopental Sodium, *Thiopentalum Sodicum Sterile*, U.S.P. (Sterile Thiopentane Soluble). A mixture of thiopental sodium with anhydrous sodium carbonate as a buffer, which meets the requirements of the Sterility Test for Solids, U.S.P.

RECTAL ANESTHESIA

The administration of anesthetics by rectum may be indicated occasionally but is seldom resorted to if other routes are available. Gwathmey's oil-ether mixture, a solution of ether in oil, is administered by rectum. In severe attacks of *asthma* the rectal adminis-

tration of ether and oil in equal parts may be useful. Rackeman (1943) has satisfactorily instilled 60 cc. of equal parts of ether and oil two and three times daily.

Tribromoethanol is regularly given by rectum. This preparation was first used for general anesthesia but was too toxic. At present it is employed largely as a basal anesthetic, especially in children.

Tribromoethanol has been reported as useful in restlessness and delirium associated with pneumonia. It is administered in dosage of 60 mg. (1 grain) per kilogram by rectum.

In tetanus many have employed tribromoethanol as a retention enema. Twenty-five milligrams per kilogram have been given as an initial dose, to be followed in fifteen to twenty minutes with about one-half that dose.

Paraldehyde has been administered rectally to produce obstetric analgesia, but its use is not too desirable. The shorter acting barbiturates including pentobarbital, amytal, and thiopental are often used rectally as basal anesthetics.

HYPNOTICS

The first essential of an ideal hypnotic is that it should produce sleep without danger. An ideal hypnotic should possess the following attributes: (1) possess no excitement stage, (2) have a smooth regular absorption, (3) be excreted promptly, (4) possess no side reactions, (5) possess a wide margin of safety, (6) be nonhabit forming, (7) develop no tolerance, (8) and finally, produce a reliable hypnotic effect.

General Action.—The general action of the hypnotics is that of a descending depression of the central nervous system, beginning with the cortex. Each compound acts with varying intensity at different points in the cortex and in subcortical regions. The more recently acquired functions of the brain are acted upon to the greatest extent by hypnotics. Pick suggests that such drugs as alcohol, paraldehyde, chloral hydrate, and the bromides, act by depressing the cerebral cortex; while derivatives of the barbituric acid group act by depressing the thalamic region. In addition to their action on the central nervous system, most of these drugs have harmful effects on other parts of the body. Hypnotics will produce complete anesthesia if given in large doses. Most hypnotics are contraindicated for general anesthesia in clinical practice because the anesthesia is too prolonged.

Classification of Hypnotics

A classification for therapeutic purposes could well be made on the basis of rapidity of onset and duration of sleep produced. On this basis of classification the following illustrations suffice: Chloral, paraldehyde (rapidly acting over a short period), sulfonethylmethane (slow acting over a long period), barbital and pentobarbital (between these). The following classification will be used:

1. **Ethane Derivatives.**
   - **Paraldehyde** $(CH_3.CHO)_3$.
   - **Chloral hydrate** $CCl_3.CH(OH)_2$.
   - **Chlorobutanol (chloretone)** $CCl_3C(OH).CH_3CH_3$.
   - **Butyl chloral hydrate** $CH_3CHCl.CCl_3.CH(OH)_2$.
2. **Sulfone Group.**
   - **Sulfonmethane (sulfonal)** $(CH_3)_2C(SO_2C_2H_5)_2$.
   - **Sulfonethylmethane (trional)** $(C_2H_5)(CH_3)C(SO_2C_2H_5)_2$.
3. **Barbituric Acid Derivatives.**

ETHANE DERIVATIVES

Paraldehyde

Paraldehyde $(CH_3.CHO)_3$ is a transparent, colorless liquid, with a characteristic odor and sharp taste. It is a polymer of acetaldehyde. It is miscible with water (1:8), alcohol, milk, and aromatic elixir. It should be carefully stored, since it tends to decompose with formation of peroxides and an increase in acidity.

Action and Uses.—Paraldehyde possesses hypnotic, sedative, and antiseptic action. It acts rapidly and produces sleep which closely resembles natural sleep; it has no analgesic action. Therapeutic doses do not cause depression of the heart or respiration. The obvious disadvantage of paraldehyde lies in its odor on the breath the following day, but this is compensated by its efficacy, and above all by the absence of toxicity. The drug is rapidly absorbed from the gut, and excreted chiefly by the lungs, and a smaller part in the urine. Since it is excreted in part by the lungs, it should be avoided in bronchitis and pneumonia as it stimulates bronchial secretion.

Toxicology.—The symptoms of acute poisoning are unconsciousness, lasting several hours, and occasionally nausea, vomiting, headache, and dizziness. Fatalities, however, are rare, recovery having taken place after taking three ounces, although the *fatal dose* may be placed at approximately 25 cc. Death may occur from paralysis of the respiratory center. *Treat* poisoning by gastric lavage, stimulation by coffee or strychnine, and by application of heat. *Post-mortem findings* are not characteristic, but there may be an odor of paraldehyde in the viscera.

This drug sometimes produces a drug habit in spite of its unpleasant taste. Symptoms of chronic intoxication are similar to those of chronic alcoholism.

Therapeutic Uses.—Paraldehyde is used as a hypnotic, sedative, and antiseptic. The drug is usually ordered alone or as the elixir. It may be administered in fruit juices. Paraldehyde may also be given by *rectum*. It is sometimes given intravenously in 1 cc. dosage to obtain its full anticonvulsant action.

In the treatment of *status epilepticus* Collier (1928) recommends paraldehyde above any other remedy; he gives up to 32 cc. (8 drachms) in an equal quantity of olive oil by rectum. In *tetanus*, 4 to 24 cc. (1-6 drachms) may be given rectally in a little physiological saline. As a sedative in *delirium tremens* paraldehyde is the hypnotic of choice; administer 12 to 16 cc. (3-4 drachms) several times daily. Recently it has been used for preoperative sedation and to produce analgesia and amnesia in childbirth. In treating *insomnia*, Fantus suggests the following prescription.

℞

Paraldehyde ---------- 60.00 cc. (f℥ij)
Sweet Orange Peel Tincture--q.s. ad 120.00 cc. (f℥iv)
M. Sig.: 1 to 4 teaspoonfuls on retiring.

Preparations

Paraldehyde, *Paraldehydum*, U.S.P. *Dosage:* 4 cc. (1 fluidrachm). Best administered with cracked ice or ice-cold liquids. B.P., 2-8 cc. (30-120 min.).

Chloral Derivatives.—Chloral hydrate is the standard hypnotic of this group. It has the disadvantages of causing cardiac and respiratory depression in overdosage and of causing gastric irritation unless

properly diluted; furthermore it cannot be used hypodermically. Its derivatives are less irritating but their hypnotic action has been decreased. Chlorobutanol can be given by hypodermic injection.

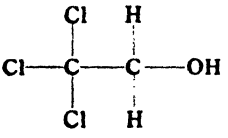
Chloral Hydrate

Chloral hydrate, which was the first synthetic hypnotic to be produced, immediately attained great popularity, and due to its indiscriminate use most of the possible dangers from its abuse were soon discovered. It was discovered by Liebig in 1832 and introduced by Liebreich as an anesthetic in 1869. It is a useful hypnotic; moderate doses induce a condition closely resembling that of normal sleep. It occurs as colorless crystals, possessing an aromatic odor and bitter taste. It is freely soluble in water and in alcohol, but is decomposed by strong alcoholic solutions. Chloral hydrate is undoubtedly the most useful of all hypnotics and the cheapest. The present tendency is toward a revival of its use.

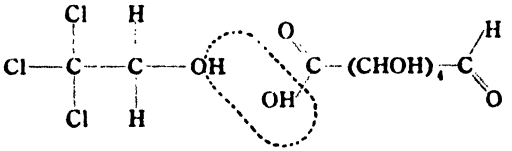
Chloral is little used, the hydrate being commonly used in medicine.

$$\underset{\text{Chloral}}{CCl_3CHO} + H_2O = \underset{\text{Chloral hydrate}}{CCl_3CH(OH)_2}$$

Pharmacological Action.—This drug possesses hypnotic, analgesic, antispasmodic, and antiseptic action. The drug is absorbed quite rapidly from the stomach and intestines. Chloral may form the nontoxic urochloralic acid (trichlor-ethyl glycuronic acid). Urochloralic acid reduces Fehling's solution and thus gives the erroneous belief that chloral causes glycosuria. A small amount of chloral is eliminated unchanged.



Chloral hydrate



Urochloralic acid

Local Action.—Chloral hydrate, like the aldehyde, is irritant to the skin and mucous membranes, and may cause vomiting if given in concentrated form. If applied to the skin it is counterirritant, producing reddening, slight anesthesia, and if concentrated, may cause destruction of the tissues. This action is due to its chlorine content.

Action on the Nervous System.—Chloral hydrate depresses the central nervous system, small doses producing a feeling of weariness followed by sleep in which the pulse and respiration are slightly slowed as in normal sleep. The reflexes are not abolished. Large doses rapidly cause narcosis and abolition of the reflexes. There is a slowing of the respiration and fall of blood pressure.

Action on Circulation.—The heart is slowed after therapeutic doses of chloral; Alstead (1936) states that chloral hydrate is a cardiac depressant only in much larger than ordinary doses. The blood pressure is little affected. In poisoning the blood pressure is reduced by weakness of the vasomotor center and the heart. The cutaneous vessels are dilated and there is a rapid fall in temperature. The chlorine content explains the poisonous action on the heart. This toxic action on the heart resembles that of chloroform, the auricles being affected first and then the ventricles.

Action on Metabolism.—After chloral there is evidence of increased protein destruction, resulting in the appearance of increased nitrogen, phosphorus, and sulfur in the urine. This action is quite characteristic of chlorine compounds of the methane group, as chloroform, etc. From the continuous use of chloral there may result fatty degeneration of the liver, heart, and arteries.

Toxicology.—Most cases of chloral hydrate poisoning are due to errors in its administration as a medicine. In a few instances the poisoning has been suicidal. The drug has been given secretly in food or drink for criminal purposes. If the drug is taken regularly, the tolerance of the body is increased and a habit may be formed.

When chloral hydrate is taken in toxic doses, signs of gastrointestinal irritation may occur. The victim may become comatose, with muscle relaxation, cold extremities, low blood pressure, convulsions, delirium, and cyanosis. The pupils become miotic. Death results from respiratory paralysis.

Chronic poisoning is characterized by variable symptoms, such as skin rashes, vesicles and ulcerations, inflammation of the eyes, nervous symptoms, insomnia, and even delirium tremens.

The *fatal dose* varies from 2 to 30 grams and death may occur in from fifteen minutes to six hours. *Treatment:* Treat acute poisoning by gastric lavage with potassium permanganate (1:1,000); keep body warm and administer oxygen and artificial respiration. Strychnine and strong coffee are indicated for stimulation.

Therapeutic Uses.—Chloral hydrate is used as a hypnotic, analgesic, and antispasmodic. Disadvantages of chloral hydrate include its pungent odor, bitter taste, and habit-forming tendencies. It may be administered internally either alone or with other agents, such as the bromides. It may be administered orally or by rectum. When administered orally, give diluted in water or cracked ice, in milk, or in tincture or syrup of orange. Externally, it may be used in ointments for treatment of pruritus and eczema.

Hypnotic.—Chloral hydrate is an efficacious hypnotic in insomnia due to nervous excitement. From the sleep produced by it the patient can wake naturally and drop off to sleep again. The drug is especially good in the early years of life. It has the peculiarity, if given to old people, of causing a type of sleep-walking in which the patient becomes active in the middle of the night, and has no memory of his wanderings. It is not so valuable if sleeplessness is due to pain. In such cases it may be combined with morphine. Given well diluted with water (0.3 to 0.6 Gm.), and in proper doses, it produces sleep within an hour, and is harmless even in heart disease.

Sedative.—It is used as a sedative in convulsions caused by strychnine, in tetanus, delirium, eclampsia, whooping cough, etc. In *tetanus* 2 to 3 grams (30 to 45 grains) are administered in olive oil or water by rectum. It is well absorbed by the rectum, and doses may be repeated every four hours. In *rabies* large doses of chloral hydrate and sodium bromide, 1.5 to 3 grams (22 to 45 grains) of each, may be given in water by rectum. It is especially valuable in conjunction with the bromides. In *delirium fever* it may be given in small doses. It is prescribed largely with other agents, such as bromides and codeine. It should not be given, however, if the heart is weak or if other measures could be used.

As sedative:

℞

Chloral Hydrate	1.5 Gm.	(gr.xxij)
Sodium Bromide	3.0 Gm.	(gr.xlv)
Orange Syrup q.s. ad	60.0 cc.	(f℥ij)

M. Sig.: Teaspoonful as required.

Skin Diseases.—Chloral hydrate may be used alone or in combination with other drugs, as camphor, salicylic acid, menthol, in making various ointments for the treatment of pruritus, eczema, warts, ringworm, dermatitis, etc.

In treatment of pruritus:

℞

Chloral Hydrate	4.00 Gm.	(3j)
Menthol	0.04 Gm.	(gr.⅔)
Petrolatum q.s. ad	30.00 cc.	(℥j)

M. Sig.: Apply locally.

Note.—Chloral hydrate is best given in well-diluted solutions. It should not be given with alcohol, as chloral alcoholate ("knockout drops") is formed.

PREPARATION

Chloral Hydrate, *Chloralis Hydras*, U.S.P., B.P. *Dosage:* 0.6 Gm. (10 grains).

Chlorobutanol, $CCl_3C(OH).CH_3CH_3$, chloretone occurs as colorless crystals possessing a characteristic musty taste. It is slightly soluble in water (1:125) and very soluble in alcohol (1:1).

Chlorobutanol is apparently absorbed unchanged from the alimentary tract, but is decomposed in the body. It possesses a local anesthetic action which is sufficient frequently to prevent vomiting. It possesses an antiseptic action fifteen times that of boric acid. Its action on the central nervous system is similar to that of chloral hydrate, and hypnotic doses are apparently as dangerous as chloral hydrate on respiration and the heart. It may not be habit forming. It is said to be useful as a mild local anesthetic in dentistry, etc., and for insomnia, vomiting, and spasmodic conditions. It is used frequently as a preservative for hypodermic solutions. *Dosage: oral*—from 0.3 to 1.3 Gm. (5 to 20 grains) in capsules; *hypodermic injection*—a saturated aqueous solution as a local anesthetic.

Butylchloral hydrate, $CH_3CHClCCl_2CH(OH)_2$, is another chlorinated hypnotic. It occurs in white laminae, and has a pungent odor and acrid taste. It is soluble in water (1:50) and in alcohol (1:1). The action of this preparation is similar to that of chloral hydrate, except that the former is said to be less depressing and more analgesic. It is recommended for the treatment of *trifacial neuralgia.*

PREPARATIONS

Chlorobutanol, *Chlorobutanol,* U.S.P. *Dosage:* 0.6 Gm. (10 grains).
Chlorbutol, B.P. *Dosage:* 5-20 gr.
Butylchloral Hydrate. N.N.R., 0.3 to 1.3 Gm. (5 to 20 grains).

THE SULFONE GROUP

Two analogous compounds formed by the substitution of sulfone radicals in methane are sulfonmethane and sulfonethylmethane. The

sulfonal drugs, such as sulfonal and trional, are effective hypnotics, but their slow absorption and delayed action have led to their replacement by the more rapidly acting hynotics, such as the barbituric acid derivatives. At present their use is largely confined to mental hospitals.

The sulfonmethanes in therapeutic doses produce sleep without noticeable effect on circulation or respiration. In large doses, acute poisoning may occur, characterized by gastrointestinal disturbances and also disturbances of metabolism and the nervous system. Cumulation may follow prolonged use.

These drugs are usually prescribed as powders. They are apparently more effective as hypnotics in insomnia unaccompanied by pain or discomfort. They have been used with some success as antispasmodics in epilepsy, hiccup, and chorea.

Sulfonmethane, or sulfonal, diethylsulfondimethyl methane, depends on ethyl radicals for its hypnotic action. Its action is increased by replacing the methyl radicals with ethyl, i.e., trional, in which one methyl group is replaced. It occurs in crystal form; it is slightly soluble in water (1:365) and somewhat soluble in alcohol (1:60).

Action and Uses.—The action is slow and irregular (four to five hours). The analgesic properties are weak. Therapeutic doses have little effect on circulation and respiration. It is eliminated slowly by the kidneys as sulfonal and ethylsulfonic acid. With repeated doses it has a tendency to accumulate.

Sulfonal is indicated in the treatment of *functional nervous insomnia.* It is of some value in reducing *night sweats* in tuberculous patients. In moderate doses it is a useful and harmless *somnifacient.* This drug is best administered in capsules, tablets, or suspended in a syrup.

Toxicology.—Death usually is accidental, resulting from taking an overdose. The toxic symptoms are headache, mental confusion, ataxia, stupor, and coma. The respiratory center is depressed slowly and death follows. In some cases, bile, albumin, casts, and blood are present in the urine. The *fatal dose* varies from 5 to 100 grams, death occurring in a few hours, or death may occur several weeks later. At *autopsy* renal irritation and congestion of the lungs may be found.

Treat acute poisoning by active purgation and by washing the stomach with warm water. Administer alkalies. Stimulants and artificial respiration may be indicated.

Sulfonethylmethane or diethylsulfonmethylethylmethane was originally introduced in medicine as trional. It is characterized by colorless crystalline scales which are slightly soluble in water (1:200) and readily soluble in alcohol. It is administered in the same manner and for the same conditions as mentioned for sulfonal.

Trional is more active as a hypnotic agent than sulfonmethane, and is quicker in its effect. It is more rapidly absorbed and excreted, and somewhat more toxic.

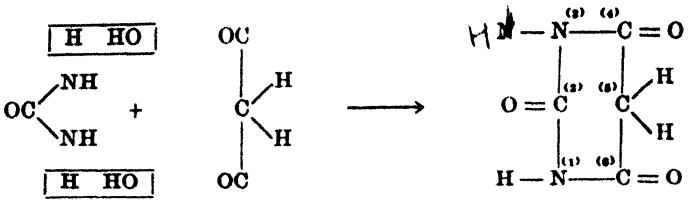
PREPARATIONS

Sulfonmethane, *Sulfonmethanum,* N.F. *Dosage:* 0.75 Gm. (12 grains).
Sulfonethylmethane, *Sulfonethylmethanum,* N.F. *Dosage:* 0.75 Gm. (12 grains).

BARBITURIC ACID DERIVATIVES

Ever since urea was prepared synthetically by Wohler in 1828, its derivatives have occupied an important place in medicine. They have largely displaced the older hypnotics and sedatives, as they are sedative but as a rule produce few serious side reactions.

Chemistry.—The barbiturates may be formed from urea and malonic acid, producing malonylurea or barbituric acid as follows:



Urea Malonic acid Malonylurea (barbituric acid)

Malonylurea (barbituric acid) acts like an acid, forming salts such as barbital, phenobarbital, etc. By replacing the hydrogen atoms at 5 by alkyl or aryl groups, compounds possessing hypnotic action are produced. If the substituting groups are chemically stable, the resulting compounds are usually more stable and longer acting in the body. If the groups contain branched chains or double bonds, these are likely to be rapidly destroyed by the body and to be obviously short acting. Replacement of the oxygen in position 2 by sulfur results in thiobarbiturates which are very short acting, e.g., thiopental sodium.

Numberless derivatives have been produced, differing chiefly in potency and rapidity of action. These compounds are fairly stable but not very soluble in water. The sodium salts of the barbiturates are readily soluble in water, but solutions are less stable and may even form toxic decomposition products. Thus, for intravenous use, the solutions should be prepared just before use.

Pharmacological Action of Barbitals.—These compounds produce sedative, hypnotic, antispasmodic, and anodyne action. They are rapidly *absorbed* from the intestinal tract and are *excreted* almost exclusively in the urine, but a large amount may be stored in the brain, liver, spleen, and kidneys. When administered intravenously they leave the blood stream in a few minutes. Compounds, such as amytal and nembutal, with unstable side chains are rapidly detoxified. In the case of barbital, 45 per cent of a therapeutic dose is excreted in twenty-four hours and 80 per cent in six days, whereas with phenobarbital only 3 per cent is excreted in twenty-four hours and 15 per cent in six days (Koppanyi, 1933). The low excretion of these drugs is a grave objection to their use in insomnia.

Location of Action.—The central depression of these drugs is thought to be located on the cerebral cortex and probably on the subcortical ganglia, especially on the hypothalamic portion of the diencephalon. The action of morphine, chloral, and the bromides is predominantly on the cortical regions.

Nervous System.—The threshold for *painful stimuli* is decidedly increased until there is no response under deep narcosis. *Reflexes* are generally depressed. Koppanyi (1933) reports that barbital is evenly distributed in different parts of the central nervous system. This refutes the statements of Keeser and Keeser (1935) who found higher concentrations in the midbrain and thalamus.

Mild doses of barbiturates generally allay nervousness and restlessness and if given at night, produce sleep. With increase in dose, analgesia, followed by amnesia and anesthesia, occurs. Small doses pro-

duce a striking change in emotional attitude; worries and mental disturbances disappear (Lindemann, 1932).

Respiration.—Large doses depress the respiratory center directly, reducing the depths and the rate, while hypnotic doses produce little effect. Intravenous administration may result in shallow and rapid respiration. Small doses given rapidly by vein may paralyze the respiratory center. In prolonged narcosis pulmonary edema may occur, followed by pneumonia.

Circulation.—Therapeutic doses given orally, hypodermically, or slowly by vein produce no significant change in circulation. Rapid administration by vein will cause a rapid fall of blood pressure, followed usually by prompt recovery.

Intestinal Tract.—The activity and tonus of the intestinal tract are diminished. The sensitiveness of the stomach is decreased, so that nausea and vomiting reflexes are depressed. It appears that the barbiturates depress the motor activity of smooth muscle by direct action on smooth muscle cells or perhaps by action on intrinsic nervous tissue.

Barbiturates in large hypnotic and anesthetic doses produce a reduction of the gastric and pancreatic secretions, with prompt return to normal flow after stopping the drug (Coffey, et al., 1940).

Other Actions.—Temperature is lowered slightly by therapeutic doses and markedly by toxic doses. Liver function is not found to be impaired by therapeutic doses.

Toxicology.—Acute poisoning by barbiturates is not infrequent, either by suicidal intent or over-susceptibility or by the therapeutic use of large doses for anesthesia, especially if given by intravenous injection. All the members of the barbital group should be administered with care. All barbiturates when used alone may produce excitement in varying degrees in a large percentage of the cases. Many deaths are reported from the barbiturates. We are not familiar with the toxicology and idiosyncrasies of all the barbital compounds, but, no doubt, they are all somewhat similar to the toxic actions of barbital and phenobarbital.

During recent years the barbiturates have been used perhaps the most commonly of all the hypnotics in cases of severe insomnia. Persons suffering from mental disorder require, and can often tolerate, much larger doses of hypnotics than normal persons. The margin between their therapeutic and toxic doses is fairly wide. The risk of habit formation is well known, although it is readily admitted that the addiction habit from these drugs cannot be compared with that of morphine or cocaine.

A sleepless patient, often suffering from physical pain, misery, and depression from continued use of these drugs, may often take an overdose not caring what happens, and perhaps "hoping for the worst." These drugs also cause amnesia, and a fatal dose could easily be taken unknowingly. Solis-Cohen and Githens state that more deaths are reported in Great Britain from the barbiturates than from any other group of drugs. These drugs should be sold under the Narcotic Law to prevent common practice of self-medication.

Acute Poisoning.—The acute type may be characterized by mental confusion, drowsiness, fall in blood pressure, coma, rapid pulse, moist skin, pulmonary edema, and collapse. The pupils are usually constricted. Some patients may develop a skin rash of the scarlatiniform, macular, or vesicular type. The cutaneous symptoms usually develop at or near the time the patient takes the drug. There may be psychic manifestations of varying types. Huddelson (1929) treated a series

of 1,147 patients, and of this group 37 per cent had gastrointestinal disturbances, nausea, vomiting, and diarrhea.

Diagnosis of Poisoning.—History of ingestion of drug. When no such history is obtained and one sees a patient in coma where reflexes and pupillary reactions, though obtunded, are obtained, and who is cyanotic, has a low blood pressure and a subnormal temperature, barbiturate poisoning must be suspected. *Hippus*, when present with the other features is diagnostic. The presence of the chemical in body fluids is confirmatory of poisoning.

Treatment.—

1. Wash out the stomach, irrespective of how long previously the drug was taken. The drug causes cessation of peristalsis, and thus much of the drug is retained for some time. Water or dilute permanganate solution is used. If the patient is in coma, the stomach should be evacuated, with the head lower than the body to prevent aspiration of fluid. The bowels should be emptied if necessary by enemas.
2. Administer oxygen continuously.
3. Administer Picrotoxin Solution, intravenously.
   a. Concentration—0.2 per cent in normal saline.
   b. Dosage— 5 mg. 1st dose—2.5 cc.
      5 mg. 2nd dose—2.5 cc. 20 minutes later.
      10 mg. 3rd dose—5.0 cc. 30 minutes later.
4. In case of a failure, administer
   a. Ampules of Camphor, N.F., intramuscularly—1 cc. = 0.2 Gm. of Camphor in Oil.
   b. Inhalation of CO_2, 5 per cent and O_2, 95 per cent.

Note: (Barbituric acid derivatives depress and paralyze the respiratory center, picrotoxin directly and camphor reflexly antagonize this action.)

5. Give glucose by vein to combat acidosis and increase diuresis.

Poole (1929) recommends that a skin test be made before administering barbiturates. He injects 0.02 cc. of a 2 per cent phenobarbital solution intradermally. A wheal and soon a small area of edema will develop in a sensitive person within half an hour.

Clinical evidence indicates that the toxicity of the more important drugs are (from low toxicity to high): pentobarbital, amytal, phenobarbital, barbital. The toxicity of the various barbitals varies, however, with method of administration, and solubility often modifies the depressant action of some of the barbital derivatives.

The following list, collected by Scarlet and MacNab (1935), represents a fairly accurate statement of the distribution of barbiturate poisoning.

Veronal	247	Dial	4
Medinal	5	Nembutal	5
Allonal	17	Amytal	5
Luminal	41	Phanodorn	1

Hambourger (1939) gives the following statement after making a study of the use of barbiturates.

"More than 1,200,000,000 grains of barbituric acid derivatives were sold in the United States in 1936. The total number of suicidal deaths by the barbiturates in the United States in 1936 was probably close to 300. The probable number in 1937 may have approached or even exceeded 400. For the five years 1932-1936 the national incidence of suicides by barbiturates represents 4.2 per cent of all poisons (except gas) and 0.66 per cent of all methods used for suicide."

Necropsy Findings.—In acute poisoning nothing characteristic may be seen grossly. When life is prolonged for a number of days there is cyanosis, congestion of the viscera, with hyperemia and edema of the meninges and perivascular hemorrhage. The heart is dilated and the lungs are congested and edematous and frequently show patches of pneumonia as a result of prolonged coma. Atelectasis and pulmonary abscess occur. The kidneys show degeneration of the convoluted tubules and petechial hemorrhages in the pelvis. The liver shows fatty degeneration. Capillary conjugation and hemorrhage may be found in the gastrointestinal tract. The brain, liver, kidneys, and spleen contain large amounts of the drug, and in fatal cases these organs should be saved for the toxicologist.

Chronic Poisoning.—Habituation to the drug is readily acquired. The symptoms of chronic poisoning are: anorexia, headache, weakness, psychoses, visual disturbances, anemia and renal damage, constipation, loss of memory, vertigo, and vague heart symptoms may be present. *Treatment* should be given at an institution. Symptomatic treatment may be indicated, such as codeine for headache, bromides for psychoses, physiotherapy, exercise, fresh air, and diet for general health.

Therapeutic Uses.—In general, barbiturates are used in securing calmness and sleep, to suppress convulsions, and for partial anesthesia. Sedative doses are not analgesic, but the addition of other analgesics renders them more effective, presumably by the reduction of apprehension of pain.

These drugs are usually administered by mouth in the form of powders, capsules, or tablets. They should be followed by hot fluids, such as milk or beef tea. Soluble barbital and soluble phenobarbital may be given intravenously or intramuscularly. Their intravenous use should be limited to conditions in which the oral route is contraindicated. The intravenous route should be used (1) if the patient is unconscious; (2) in general anesthesia; (3) in delirium, and (4) in conditions in which prompt action is of primary importance. Solutions of the soluble compounds break down too rapidly to enable them to be prescribed in bottle form. When the soluble salts are administered in capsules, they seem to accentuate the period of mild excitement which often precedes barbiturate hypnotic action; thus they have no advantage over the insoluble forms.

When administered intravenously, by rectum, intramuscularly, or intraperitoneally, the soluble salts are employed in 5 to 10 per cent physiological saline solution. Intramuscular or subcutaneous injections are likely to be followed by local irritation.

Hypnotic.—The barbital compounds are employed to produce sleep, particularly when insomnia is not the result of pain. Barbital or phenobarbital produces six to eight hours of sleep with little after effect except when given in large doses. With other barbiturates, such as pentobarbital, the action is shorter—three to six hours.

For insomnia:

℞

Barbital ---------- 2.00 Gm. (℈ss)

Pone in capsulas No. vj.

Sig.: One in hot milk at bedtime.

As a Sedative.—Barbiturates are extensively used to allay nervous apprehension. In nervous vomiting of pregnancy 0.06 to 0.12 gram (1 to 2 grains) an hour before feeding and at bedtime is indicated. In maniacal conditions, such as delirium tremens, pentobarbital or sodium amytal may be given in doses of 0.24 to 0.48 gram (4 to 8 grains).

A *sedative often brings prompt relief in case of colic in infants.* Sodium phenobarbital is the sedative of choice (Neff, 1940); it may be given safely, basing the dosage on the age of the child. Administer regularly every four hours for several days if necessary. In writing the prescription, the physician should remember that an ounce of the usual liquid makes only 6 or 7 teaspoonfuls of standard size.

As sedative in colic:

℞

Phenobarbital (sol.)	0.25-0.40 Gm.	(gr.iiiss-vss)
Peppermint Water	15.00 cc.	(f℥ss)
Aromatic Elixir q.s. ad	90.00 cc.	(f℥iij)

M. Sig.: One teaspoonful every four hours before feeding.

In the Treatment of Epilepsy.—Phenobarbital should be used first in the treatment of adults with *grand mal* attacks because of the high index of therapeutic efficiency and the relatively low toxicity of the drug. *Dosage:* In treatment with phenobarbital a reservoir of the drug is established in the system and kept at a constant level by frequent administration. Since excretion is slow this can be accomplished by administering the drug once or twice daily. The initial dose for an adult should be at least 1½ grains (0.1 Gm.) daily. Increase dose to 2¼ grains (0.15 Gm.) daily if the smaller dose is ineffective. If attacks continue further, increase of ¾ grain (0.05 Gm.) increments can be made until a maximum of 6 grains (0.4 Gm.) three times daily is reached.

Barbiturates may be used in all forms of *convulsions, tetanus, strychnine poisoning, eclampsia, cocaine poisoning,* and *insulin overdosage.* The dose is the same—0.24 to 0.48 gram (4 to 8 grains) of pentobarbital or 0.42 to 0.72 gram (7 to 12 grains) of amytal given slowly by vein.

As an Analgesic.—Barbiturates are often administered with other drugs for relief of pain.

Amnesia and Analgesia in Obstetrics.—As soon as the patient enters the hospital, preferably before the pains are too strong, 0.4 to 0.5 gram (6 to 7½ grains) of pentobarbital may be given orally. At the same time 0.0004 gram (1/150 grain) of scopolamine should be given hypodermically. These drugs act rapidly and, if the room is darkened, the patient should sleep between pains. None of the barbitals can be regarded as ideal for obstetrical use.

Migraine, Neuritis, Neuralgia.—Barbital is especially valuable in the treatment of headache, neuralgia, and various nervous disorders.

For migraine:

℞

Barbital		
Acetophenetidin		
Acetylsalicylic Acid	ãã 0.65 Gm.	(gr.x)

Ft. cap. No. vj.

Sig.: One every two hours as required.

Anesthesia.—Barbiturates are rarely employed as the chief anesthetic agent because of the prolonged sleep, lack of control of the agent when it is once given, and because of the risk of pulmonary complications. Safety can be attained by small doses supplemented by volatile anesthetics.

Premedication.—Amytal and pentobarbital are indicated as preanesthetic sedatives. On account of its unusually wide margin of safety,

nembutal is considered by some the best, especially as a preliminary drug to nitrous oxide or ethylene. It may be given orally, rectally, and intravenously.

Procedure: Administer the barbiturate the evening preceding the operation, to insure rest. If pentobarbital sodium is used, give in capsules, 0.1 Gm. (1½ grains). Give a second dose 0.1 to 0.2 Gm. (1½ to 3 grains) two hours before operation, and repeat one hour before the operation if necessary. The last dose is usually accompanied by 10 mg. (⅙ grain) of morphine, and 0.4 mg. (1/150 grain) of atropine, hypodermically.

In local anesthesia the barbiturates have the additional advantage of being prophylactic against acute poisoning by cocaine and procaine.

IMPORTANT BARBITURIC ACID DERIVATIVES

There are a hundred or more barbituric acid derivatives. All of these compounds augment the action of analgesics and possess a wide margin of safety, but they are slower acting than chloral hydrate. They produce no irritation. Barbital, barbital sodium, pentobarbital sodium (nembutal) and phenobarbital (luminal) are widely used barbiturates. Thiopental (pentothal) is used almost exclusively for intravenous anesthesia.

Barbital and Barbital Sodium

Barbital, or veronal, is a white, crystalline powder, soluble in water (1:150) and in alcohol (1:14). Barbital, 8 to 10 grains, administered in a hot liquid is an efficient hypnotic. It promotes rapid action, induces normal sleep, does not affect the heart, circulation, or kidneys, and is free from after effects. Small doses induce sleep, apparently with little other effect, and are relatively safe. Large doses have caused death. Skin eruptions from repeated use of this drug are common.

Barbital is *excreted* slowly in the urine; thus repeated administration may result in poisoning. It should not be administered for longer than a week at a time. Barbital may be given in pills, tablets or capsules.

Barbital sodium is soluble in water (1:15). It is rapidly absorbed, and rapidly excreted. Soluble barbital may be given by mouth, by rectum, or hypodermically. It is preferably given by mouth. In emergency cases the sodium salt may be injected intravenously. Its actions and uses are the same as those of barbital.

Preparations

Barbital, *Barbitalum,* U.S.P. *Dosage:* 0.3 Gm. (5 grains). *Barbitonum,* B.P., 0.3-0.6 Gm. (5-10 grains).

Barbital Sodium, *Barbitalum Sodicum,* U.S.P. *Dosage:* 0.3 Gm. (5 grains). *Barbitonum Solubile,* B.P., 0.3-0.6 Gm. (5-10 grains).

Barbital Sodium Tablets, *Tabellae Barbitali Sodici,* U.S.P. *Dosage:* 0.3 Gm. (5 grains).

Phenobarbital and Phenobarbital Sodium

Phenobarbital, or luminal, in doses of one to three grains, produces sleep without depression of respiration or circulation, and does not harm the kidneys or stomach. Phenobarbital is used as a hypnotic in nervous insomnia and in conditions of excitement of the nervous system, such as chorea, and in neurasthenia, cardiac and gastric neuroses, climacteric disorders, dysmenorrhea, and preoperative and

postoperative cases. It is used with excellent success as a sedative and antispasmodic in epilepsy. It is a white bitter powder insoluble in water. It is best administered in capsules or powders.

Phenobarbital sodium has actions and uses similar to those of barbital but has the advantage of being soluble in water and alcohol. Enormous doses have been given. The drug in large doses kills by respiratory paralysis. No renal injuries or gastric disturbances have been observed following its use.

Sodium phenobarbital may be administered hypodermically in the form of a 20 per cent solution, prepared by dissolving the salt in boiled and cooled distilled water. It may be given hypodermically in doses of 0.1 to 0.3 Gm. (1½ to 5 grains). *Caution.*—Aqueous solutions are not stable on standing; on boiling, a precipitate occurs.

Phenobarbital and soluble phenobarbital may be administered over long periods of time without cumulative poisoning. Prolonged use, however, may cause development of skin rashes.

Preparations

Phenobarbital, *Phenobarbitalum*, U.S.P. (Phenylethylmalonylurea, Phenobarbitone). *Dosage:* 30 mg. (½ grain). *Phenobarbitonum*, B.P. *Dosage:* 0.03-0.12 Gm. (½-2 grains).

Phenobarbital Sodium, *Phenobarbitalum Sodicum*, U.S.P. *Dosage:* 30 mg. (½ grain). *Phenobarbitonum Solubile*, B.P. *Dosage:* 0.03-0.12 Gm. (½-2 grains).

Phenobarbital Elixir, *Elixir Phenobarbitali, U.S.P.* Phenobarbital (0.4%) in sweet orange peel tincture, amaranth tincture, alcohol, glycerin, syrup and distilled water. Alcohol content about 14 per cent. *Dosage:* 4 cc. (1 fluidrachm).

Phenobarbital Tablets, *Tabellae Phenobarbitali*, U.S.P. Usual size contains 15 mg., 30 mg., and 100 mg.

Phenobarbital Sodium Tablets, *Tabellae Phenobarbitali Sodici*, U.S.P. The usual sizes contain 30 mg. and 100 mg.

Amytal and Sodium Amytal

Amytal, or iso-amylethyl barbituric acid, is a white, crystalline substance, soluble in alcohol and slightly soluble in cold water. It produces a hypnotic effect which comes on more rapidly than that of either barbital or phenobarbital, but the effects are of shorter duration. The effects of barbital persist for from twenty-four to forty-eight hours, of phenobarbital from thirty-six to seventy-two hours, while those of amytal persist for only twelve to eighteen hours. It is given orally as a *sedative* in water or hot milk, 0.02 to 0.04 gram (⅓ to ¾ grain), two or three times daily; as a hypnotic, 0.1 to 0.3 gram (1½ to 5 grains) may be administered one-half hour before retiring. For *premedication* (because of its shorter duration of action) 0.2 to 0.6 gram (3 to 10 grains) should be used. As an *antispasmodic* in tetanus, 0.4 to 0.8 Gm. (6 to 12 grains) may be required to control convulsions.

Amytal Sodium is similar to amytal but is soluble in water. It is probably used for *premedication* to anesthesia more than all the other barbiturates combined. The profuse sweating with ether alone is absent when sodium amytal is used. The pupils remain moderately contracted. Idiosyncrasies are rare, but its use is not advised in old and debilitated persons. It may be used intravenously, intramuscularly, subcutaneously, orally, and rectally. The sedative dose

is 0.2 gram (3 grains) repeated every six hours. For premedication, 0.2 to 0.6 gram (3 to 10 grains).

PREPARATIONS

Amytal, N.N.R. *Dosage:* 0.02 to 0.04 Gm. (⅓ to ¾ grain) as sedative; 0.1 to 0.3 Gm. (1½ to 5 grains) as hypnotic.

Amytal Sodium, N.N.R. *Dosage:* As sedative or hypnotic 0.2 Gm. (3 grains), repeated if necessary at intervals of six hours.

Pentobarbital Sodium (Nembutal)

Pentobarbital Sodium, nembutal, or sodium ethyl (1-methylbutyl) barbiturate, is an excellent short-acting drug, the duration of action being from three to six hours, with some degree of effect lasting for from six to twelve hours. It is a white crystalline powder, soluble in water. When given orally or rectally, postoperative sequelae are less marked. The blood pressure falls less than with amytal or pernocton.

It may be used as a sedative prior to *local, general,* or *spinal anesthesia.* For these purposes it should be administered only by those familiar with its use. It may be administered by mouth or rectum; it may be given by vein only in conditions in which oral administration is contraindicated, because the patient is unconscious as in cerebral hemorrhage, eclampsia or similar conditions, or because very prompt action is necessary. It is used in dosages of 0.097 to 0.195 gram (1½ to 3 grains), given orally thirty to forty-five minutes before operation. For *hypnotic* use, 0.1 gram (1½ grains) is indicated. Rectally, for analgesia: for infants up to 1 year, 0.03 Gm. (½ grain); up to 3 years, 0.06 Gm. (1 grain); for adults, 0.32 to 0.38 Gm. (5 to 6 grains) dissolved in a little water.

PREPARATION

Pentobarbital Sodium, *Pentobarbitalum Sodicum,* U.S.P. *Dosage:* 0.1 Gm. (1½ grains).

Pentobarbital Sodium Capsules, *Capsulae Pentobarbitali Sodici,* U.S.P. Usual sizes contain 30 mg. and 100 mg.

Pentobarbital Sodium Tablets, *Tabellae Pentobarbitali Sodici,* U.S.P. Usual sizes contain 30 mg., 50 mg., and 100 mg.

OTHER BARBITURIC ACID DERIVATIVES

Alurate and Sodium Alurate.—Alurate and sodium alurate have essentially the same action as barbital, but are used in correspondingly smaller doses. For mild cases of insomnia, 65 mg. of alurate may be given at bedtime. In obstinate cases, 0.13 Gm. may be given. The *soluble alurate,* sodium alurate, is useful for oral or rectal administration, particularly in premedication. For premedication use 1 grain per 15 pounds of body weight (10 mg. per kg.). One-third of this dose is given twelve hours before operation; the remainder, two hours before operation.

Dial, diallylbarbituric acid, occurs as a fine white crystalline powder, with a bitter taste, slightly soluble in cold water and very soluble in alcohol. The actions and uses are essentially the same as those of barbital, but dial is more active than barbital, and it is used in correspondingly smaller doses. Therapeutic doses act on the higher centers of the brain and have no untoward action on respiration or circulation. The hypnotic action is induced from one-half to one hour. *Dosage:* sedative—0.03 Gm. (½ grain) three or four times daily; hypnotic—0.1 to 0.3 Gm. (1½ to 4½ grains) one-half to one hour before sleep is desired.

Hexobarbital Soluble (Evipal Sodium), see under Intravenous Anesthetics.

Probarbital Calcium (Ipral Calcium).—Calcium ethylisopropylbarbiturate has a therapeutic nature like that of barbituric acid. It is soluble in water (1:40), but insoluble in alcohol. It is rapidly absorbed. Therapeutic doses affect only the higher centers, with little effect on the heart or circulation. It is used as a hypnotic to combat restlessness and insomnia. It is claimed that tolerance to the drug develops very slowly. Its action may persist to produce hypnotic action the following evening after the first administration. *Dosage:* From 0.12 to 0.25 Gm. (2 to 4 grains) followed by a cupful of hot water.

Probarbital Sodium (Ipral Sodium) is the sodium salt of 5-ethyl-5-isopropylbarbiturate. It has the therapeutic properties of barbituric acid. It is soluble in water and promptly absorbed and rapidly excreted. It is indicated as a hypnotic to combat restlessness, irritability, and sleeplessness. Its action is thought to be quite persistent, and tolerance to its use is not readily developed.

Neonal.—Neonal, or butylethylbarbituric acid, is three times as active as barbital. It is a white crystalline powder soluble in alcohol (1:5), but insoluble in cold water. It accentuates the action of analgesics when administered in doses of 0.05 to 0.4 Gm. (¾ to 6 grains).

Nostal, or 5-isopropyl-5-β-bromallyl barbituric acid, possesses actions and uses essentially the same as barbital. *Dosage:* As a sedative: 50 mg. to 0.1 Gm. As a hypnotic: 0.1 to 0.3 Gm.; for children, 50 mg. to 0.1 Gm. according to age. Administer with a hot drink.

Ortal Sodium, or sodium 5-ν-hexyl-5-ethyl barbiturate, has actions and uses essentially the same as those of barbital, but ortal sodium is more active than barbital and is used in correspondingly smaller doses. *Dosage:* From 0.2 to 0.4 Gm. (3 to 6 grains) with glass of hot water.

Pernoston, *5-sec.* butyl-5-β-bromalyl barbituric acid, is a powerful hypnotic which has twice the strength of sodium amytal. It is rapidly absorbed and quickly destroyed by the body. It is used to combat insomnia due to emotional strain and nervous irritability. Therapeutic doses are apparently not harmful to the vital organs. One tablet (3 grains) in a warm drink, one-half hour before sleep is desired, is recommended. It is also recommended for premedication by the intravenous route. The dose should be 0.7 to 0.8 mg. per Kg. of body weight.

Pernoston Sodium, the sodium salt of pernoston, possesses effects like those of pernoston, but the effects are induced almost immediately after injection. It is used when oral administration is contraindicated.

The contraindications are those of the ordinary barbiturates plus congestive heart failure, anoxia from pulmonary disease, asphyxia, anemia, and respiratory disturbances from diseases of the central nervous system. *Dosage:* One cc. of a 10 per cent solution (ampuls) per 12.5 Kg. of body weight by vein at the rate of 1 cc. per minute. The intramuscular dose is the same as by vein.

Phanodorn.—Phanodorn, cyclobarbital, is similar to barbital in that it accentuates the action of analgesics. It is a white, crystalline powder soluble in alcohol (1:5), but insoluble in water. It is indicated for sedative action in nervous insomnia, psychoses, and kindred ailments. Elimination is rapid, and the effect does not last long. *Dosage:* From 0.1 to 0.4 Gm. (1½ to 6 grains).

Sandoptal, or 5-isobutyl-5-allyl barbituric acid, possesses the action and uses as ascribed to barbital. *Dosage:* for mild insomnia, 0.2 Gm.; for obstinate cases of insomnia, 0.4 to 0.8 Gm.

Seconal Sodium, sodium allyl (methyl propyl carbonyl) barbiturate, is a short acting barbiturate, possessing actions and uses not unlike those mentioned for barbital. It is more active than barbital and is administered in corresponding small doses. *Dosage:* The average adult dose is from 0.1 to 0.2 Gm. (1½ to 3 grains). Smaller doses are sedative while larger doses are hypnotic. The dose for use in *obstetrics* is 3 or 4½ grains (0.3 Gm.) followed by 1½ to 3 grain doses at intervals up to a total of not more than 12 grains within twelve hours. *Preanesthetic Agent*—3 to 4½ grains one-half to one hour before administration of general anesthetic.

Vinbarbital Sodium is sodium 5-ethyl-5-(1-methyl-1-butenyl) barbiturate. The indications are much the same as for barbital. It has a short period of induction and a moderate duration of action. Its toxic reactions are much the same as the other barbiturates. *Dosage:* 32 mg., repeated three to four times daily, is the *sedative* dose; as a sedative and hypnotic, 0.1 Gm. to 0.2 Gm.; as a preoperative hypnotic, 0.1 Gm. to 0.2 Gm.; in psychiatric cases, 0.1 Gm. to 0.4 Gm.; for obstetric sedation and amnesia, 0.2 Gm. to 0.4 Gm. with or without scopolamine. Give children correspondingly smaller doses.

Relative Efficiency of Barbituric Drugs

Unfortunately it is extremely difficult to estimate the relative merits of the barbiturates, because much of the evidence is unreliable and conflicting. Grabfield believes that none of the barbiturates is superior to barbital.

Phenobarbital and soluble phenobarbital produce a longer action than other barbiturates, and hence are indicated for the treatment of

TABLE IX

ACTION	DRUG	DOSE	
		GRAM	GRAIN
Long	Phenobarbital (Luminal)	0.03-0.12	½-2
	Barbital (Medinal) (Veronal)	0.3 -0.6	5-10
Intermediate	Neonal	0.06-0.1	1-1½
	Dial	0.1 -0.3	1½-5
	Probarbital Calcium	0.12-0.25	2-4
	Probarbital Sodium	0.12-0.25	2-4
	Alurate	0.06-0.13	1-2
	Nostal	0.05-0.1	¾-1½
	Amytal	*0.02-0.3	⅓-5
	Sandoptal	0.2 -0.8	3-12
Short	Pentobarbital (Nembutal)	0.1 -0.2	1½-3
	Phanodorn	0.1 -0.4	1½-6
	Seconal Sodium	0.1 -0.2	1½-3
	Ortal-sodium	0.2 -0.4	3-6
Ultra short	Hexobarbital Sodium	0.25-0.5	4-8
	Thiopental (pentothal)	†0.1 -0.15	1½-2

*Sedative to hypnotic.

†Injected intravenously in 5 per cent solution in 10 to 15 seconds.

epilepsy. Barbital and soluble barbital have a slightly shorter action, and are widely used as hypnotics. Amytal and nembutal (pentobarbital) are short-acting drugs and are indicated for premedication. Hexobarbital and thiopental are very rapid-acting barbiturate. *See Intravenous Anesthesia.*

Tatum classifies the barbiturates according to the duration of action. While there are borderline cases, this classification is sufficiently practical to be of value to clinicians. This classification, slightly modified, is shown in Table IX.

SEDATIVES

Sedatives are drugs which allay excitement and reduce motor activity without necessarily inducing sleep. Small doses of hypnotics usually produce sedative action. The line of demarcation between hypnotics and sedatives is not definite by any means. The following drugs will be discussed under sedatives: bromides, compounds containing bromine, cannabis, scopolamine, hydantoin derivatives, and tridione.

BROMIDES

The bromides were introduced for the treatment of epilepsy in 1853 and have since enjoyed an important place in drug therapy.

Pharmacological Action.—Bromides are sedative, hypnotic, anodyne, and antispasmodic. They are rapidly *absorbed* from the stomach and intestines, and are *excreted* almost entirely in the urine. The drug is chiefly eliminated in the saliva, sweat, and milk. The administration of eight grains per day for two weeks may establish an equilibrium in which absorption and excretion are equal. When equilibrium is reached, one-fourth to one-third of the chloride in the serum has been replaced by bromide. The administration of sodium chloride therefore accelerates the elimination of the bromides. The urine, following the use of bromides, shows an excessive amount of chlorides. When bromides are given continually, hydrobromic acid is said to appear in the gastric juice.

Action on the Nervous System.—Bromides cause a general depression of the entire nervous system, except the medulla.

Action on Cerebrum.—Therapeutic doses cause the special senses to become less keen, the mind to become dull, and the sense of pain diminished. Large doses produce drowsiness and sleep. Sleep after large doses is not refreshing and is followed by drowsiness. Bromides are not directly hypnotic in the same way as morphine, but permit sleep by depressing the sleep center and excluding disturbing stimuli. After administration of bromides the motor areas of the cerebrum are depressed, voluntary movement becomes sluggish, and cerebral convulsions of epilepsy are often prevented.

Action on Respiration.—Therapeutic doses have little effect on the nervous system but large doses depress the cough reflex and lessen the tone of the respiratory muscles.

Spinal Cord.—The spinal cord is depressed as shown by diminished reflexes. The effect of bromides is opposite that of strychnine; there is some evidence that the site of action may be the same. The depression of the reflexes lowers the general muscular tone throughout the body; there is depression of the sexual reflex but not of the bladder reflex. The reflexes are reduced, and in man, the drug abolishes the induction of nausea and vomiting caused by reflex stimulation of the back of the throat.

Action on Circulation.—Therapeutic doses have little effect on the circulatory system. Large doses depress the heart and the vasoconstrictor center. Potassium bromide, given by vein, depresses the heart due to the potassium ion, a heart depressant. When given by mouth, potassium bromide has little effect on the heart because of rapid excretion.

Mechanism of Bromide Action.—A theory has been suggested by Wyis that bromides act by displacing chloride from the body. The theory does not adequately explain the action. There is considerable direct evidence that the bromine ion acts on the nervous system. Greater bromide action is obtained by decreasing the chlorides in the diet which tends to aid in the elimination of the bromine ion. One observer found that all inorganic bromides had a characteristic action in animals, an action that was absent when organic bromides and bromates were used.

Toxicology.—*Acute Poisoning.*—The clinical picture of bromide intoxication is essentially an organic reaction type; however, the symptoms vary, depending on the psychic make-up of the patient. The patient is usually in an enfeebled state. The breath has a sweetish odor, the tongue is coated, and speech is thick and slurred. Ataxia and incoordination are usually present. The pupils are usually dilated and sluggish to light. They react to accommodation. Tachycardia (120 to 140) is frequent and a temperature of 100° to 103° F. is often present. Reflexes may be sluggish or even absent in severe cases. Occasionally, a bromoderma is present, and any sudden onset of acneform lesions should at once cause one to suspect bromoderma. Memory impairment, delirium, and disorientation may accompany bromide toxicity.

Treatment of Acute Poisoning.—Therapy of bromidism consists of discontinuing bromides, forcing fluids, and giving an adequate diet and additional sodium chloride. In severe cases administer large amounts of sodium chloride. Parenteral saline is indicated in severe cases. Treatment should correct the dehydration and malnutrition as well as eliminate bromides and restore chlorides to the body. Later, attention should be directed to an underlying mental disorder so characteristic of bromidism. Blood levels above 150 mg. per 100 cc. constitute the toxic zone, although some patients are poisoned with lower levels and a few can tolerate much higher concentrations.

Prognosis.—The mortality rate is well under 1 per cent. Most deaths are due to pneumonia as a complication.

Chronic Bromide Poisoning.—Long-continued use of the bromides in large doses leads to serious mental depression and nutritional disturbances. The usual signs of such disturbances are: foul breath and coated tongue, acne or other characteristic skin lesions, mental dullness, slowing of speech, slow pulse, and ataxia. This condition is fairly common. There may be psychic difficulties and some behavioristic peculiarities. The skin lesions are usually papular in form and have a predilection for the face, back of neck, and shoulders. *Treat* by stopping drug and administering sodium chloride. Administer 6 to 8 grams of sodium chloride by mouth. In the early stages of the delirium, omit sodium chloride, as it liberates bromides, making the condition worse.

Some patients develop toxic symptoms early and are unable to take the drug regularly on account of the skin lesions or effect on the intellect, yet others may take the drug for years with no apparent ill effects. Archinaud reported a case in which the patient had taken 45 grains a day for twenty years without inconvenience or apparent ill effects.

Therapeutic Uses.—The bromides are used to depress the nervous system in conditions such as epilepsy, to allay nervous vomiting, and to

decrease sexual hyperesthesia. They are also a valuable aid in the management of tension states, anxiety, and insomnia. They have been extensively used in the treatment of epilepsy, although recently they have been replaced to a large extent by phenobarbital and dilantin.

The bromides may be administered either by mouth or by rectum. When diluted, the bromides are fairly palatable, but they are best prescribed in solution in prescriptions containing peppermint water, aromatic elixir, etc. Milk entirely disguises the taste of the drug.

Sedative.—Bromides are chiefly used as sedatives to produce sleep when insomnia is due to worry, excitement, or pain. Their pain-relieving quality is limited, but they are combined with more active anodynes, such as codeine, for synergistic action. They are often prescribed with chloral hydrate to induce sleep or to relieve convulsions. In the treatment of *status epilepticus* bromides may be given in a large dose of 4 to 5.3 grams (60 to 80 grains).

The bromides of potassium, ammonium, and sodium are identical in action except for the ammonium ion which causes a somewhat greater stimulation. The potassium ion depresses the heart, while the sodium ion is neutral in effect. Ammonium bromide liberates bromide on exposure to air, which is a serious objection. The long-continued use of bromides, as in epilepsy, may disturb the cation balance of the body, thus a mixture of bromides ($KBr:NaBr:NH_4Br$) may be of value. Potassium bromide is useful for quieting nervous excitability in neurasthenia and hysteria.

In the treatment of *skin diseases,* the bromides, preferably a mixture of the salts of sodium, potassium, and strontium, are the most satisfactory (Sutton). Fairly large doses (2 to 7 Gm.) with plenty of water, every three to six hours, should be given until physiological effects are secured. It is unwise to continue the administration of this comparatively harmless agent over long periods of time.

As sedative:

℞

Sodium Bromide	8.00 Gm.	(℥ij)
Aromatic Elixir q.s. ad	30.00 cc.	(f℥j)

M. Sig.: Teaspoonful in water every three hours as required.

For whooping cough (pertussis):

℞

Sodium Bromide	4.00 Gm.	(℥j)
Chloral Hydrate	4.00 Gm.	(℥j)
Orange Syrup q.s. ad	60.00 cc.	(f℥ij)

M. Sig.: One teaspoonful for a *child of 4 years.*

Epilepsy.—Bromides are especially indicated in epilepsy. In recent years phenobarbital has been successfully used. For epilepsy, convulsions, tetanus, and strychnine poisoning a dose of 15 grams (½ ounce) is administered by mouth or by rectum. To prevent epileptic convulsions doses of 6 to 10 grams (90 to 150 grains) may be used daily for years.

MIGRAINE.—The continuous administration of bromide is often used. Bechterew's prescription:

℞

Sodium Bromide	30.00 Gm.	(℥j)
Fowler's Solution	4.00 cc.	(℥j)
Infusion of Adonis Vernalis q.s. ad	500.00 cc.	(oj)

M. Sig.: One tablespoonful three times a day after meals.

NOTE: From time to time a blood bromide determination should be made and the amount in the blood should not exceed 175 mg. per cent. Pigmentation of the skin and keratosis should be watched for and also any other indications of arsenical intoxication.

Antemetic.—Bromides are indicated to check vomiting in seasickness and in sickness of pregnancy.

Anaphrodisiac.—As an anaphrodisiac to lessen sexual hyperesthesia such as found in chordee, following circumcision, etc., bromides are indicated in doses of 2 to 4 grams (30 to 60 grains).

Pyelography.—Recently sodium bromide has been used in x-ray therapy. It causes less discomfort than the iodides and gives good results.

The widespread use of bromides has prompted a study of the comparison of bromides and barbiturates (Barnett, 1939). It would appear that bromides are to be preferred for sedation because:

1. Margin of safety greater for bromides.
2. Recovery is more rapid and complete after bromide administration.
3. Bromides do not produce tolerance or habit formation.

PREPARATIONS

Sodium Bromide, *Sodii Bromidum*, U.S.P., B.P. *Dosage:* 1 Gm. (15 grains).

Three Bromides Elixir, *Trium Elixir Bromidorum*, N.F. Bromides of ammonium, potassium, and sodium (each 8%) in aramanth solution and compound benzaldehyde elixir. Absolute alcohol content about 4 per cent. *Dosage:* 4 cc. (1 fluidrachm).

Sodium Bromide Elixir, *Elixir Sodii Bromidi*, N.F. Sodium bromide (17.5%) in syrup, water, and aromatic elixir. Absolute alcohol content about 6 per cent. *Dosage:* 4 cc. (1 fluidrachm).

Potassium Bromide, *Potassii Bromidum*, U.S.P., B.P. *Dosage:* 1 Gm. (15 grains).

Ammonium Bromide, *Ammonii Bromidum*, N.F. *Dosage:* 1 Gm. (15 grains).

COMPOUNDS CONTAINING BROMINE

Synthetic compounds containing bromine have been produced, hoping to secure the sedative action of the bromide ion without the objectionable effects of the alkali bromides. These compounds slowly split off bromine ions in the system by oxidation of the organic substance with which it is combined, but bromine may be so firmly bound as not to exert its typical effects. The introduction of bromine into compounds already possessing hypnotic or sedation powers may result in increasing the efficiency of these compounds.

Carbromal, bromdiethylacetylurea, $(C_2H_5)_2CBr.CO.NH.CONH_2$, is an efficient and prompt sedative, reducing excitement and promoting sleep in conditions in which a powerful hypnotic is not required. In therapeutic doses it produces a restful sleep, dreamless and free from unpleasant side effects and sequelae. Such doses are said to exert no unfavorable action on respiration or heart action.

Carbromal is indicated as a sedative and mild hypnotic in neurasthenia, hysteria, neurosis with tachycardia, chorea, insomnia due to various internal diseases, mental disorders, and similar conditions.

Dosage: sedative—from 0.3 to 0.6 Gm. (5 to 10 grains) in water, three or four times daily if necessary; *hypnotic*—from 0.6 to 1.3 Gm. (10 to 20 grains) in hot water or tea.

Bromural, 2-monobromisovalerylurea, $(CH_3.CH(CH_3)CHBr.CO)\ HN.CO.NH_2$, is a nerve sedative indicated in mild cases of insomnia. It is especially useful as a nerve sedative and hypnotic in functional nervous disease. Its action lasts for from three to five hours without producing any marked effect on circulation or respiration. Bromural is ineffective in cases of insomnia associated with pain, cough, or delirium. *Dosage.*—Nerve sedative—0.3 Gm. (5 grains), three times daily; hypnotic at bedtime—0.6 Gm. (10 grains) repeated if necessary.

PREPARATIONS

Carbromal, *Carbromalum,* N.F. *Dosage:* 0.5 Gm. (8 grains).
Bromural, N.N.R. *Dosage:* sedative, 0.3 Gm. (5 grains); hypnotic, 0.6 Gm. (10 grains).

CANNABIS (MARIHUANA)

Cannabis is the dried flowering tops of the pistillate plants of *Cannabis sativa* Linné. *Cannabis indica* is a variety of common hemp preferred for medicinal uses. An oil, *cannabinol,* has been found to contain the active principle. Cannabinol is soluble in alcohol but not in water.

In Mexico and Latin America there has been widespread use of *Cannabis americana* under the name of marihuana. Hashish is another name for this drug. This name is supposed to be derived from the name Hassein, "the old man of the mountain," who recruited his robber band by employing this drug to intoxicate travelers and get them in his power. The most common method of using the drug has been in the form of cigarettes. The use of the drug has spread rapidly throughout the United States since 1935.

Pharmacological Action.—The mode of action of cannabis is poorly understood and the effects are unpredictable. It usually acts as a descending depressant of the central nervous system, producing in some respects a state resembling alcoholism, with, however, a much greater tendency toward disorientation and dissociation of personality. The exaggeration of time and space is a characteristic of this drug.

Euphoria or apprehension may be experienced from the use of this drug. Some of the sensory perceptions are made hypersensitive while others are depressed. Some persons experience a marked sexual stimulation.

Toxicology.—The after effects of cannabis are apparently not disturbing. There are frequent instances of headaches following moderate doses. Death is rare even from the taking of large quantities. No specific *treatment* is recommended for acute poisoning other than a through gastric lavage followed by a laxative. ***Habituation*** to cannabis does not occur in the same manner as it does in the case of cocaine, but it apparently occurs.

Therapeutic Uses.—Except for its use as a coloring agent in corn cures, cannabis is of little use in therapy.

SCOPOLAMINE (HYOSCINE)

Scopolamine or hyoscine ($C_{17}H_{21}NO_4$) is an alkaloid obtained from various plants of the family solanaceae, including *Atropa belladonna,*

Hyoscyamus niger and others. Although discovered separately, hyoscine and scopolamine are identical chemically. Hyoscine or scopolamine differs slightly from atropine in its formula.

Pharmacological Action.—Hyoscine possesses sedative, antispasmodic, anodyne, deliriant, and mydriatic action. Hyoscine resembles atropine in its influence on nerve endings, but differs from it in having a sedative instead of a stimulating effect on the brain. Ordinarily, little or no cardiac acceleration is induced by scopolamine. Moderate doses stimulate the vasomotor center, a large dose depresses this center. Large doses depress the respiratory center. Scopolamine instilled in the eye acts like atropine but more rapidly. The drug should be employed with caution, as it may induce a rapid fall of blood pressure and collapse.

Toxicology.—Hyoscyamus preparations are all toxic. Idiosyncrasies are common. The toxic symptoms resemble those of belladonna, but there is a greater tendency to the development of acute mania or wild delirium. Treat poisoning by removing the poison by emetics or by stomach tube. Tannic acid may be given as an antidote. Pilocarpine, ¼ grain (0.015 Gm.), and caffeine and sodium benzoate, 5 grains (0.3 Gm.), or hot coffee may be given. Pilocarpine is of no value in antagonizing the central action of scopolamine. Chloral hydrate, 10 grains (0.6 Gm.), is indicated in delirium.

Therapeutic Uses.—*Cerebral Sedative.*—Hyoscine is used as a cerebral sedative in many forms of insanity; it is not used routinely in the better hospitals for this purpose. It is used as a synergist to chloral, bromides, and other analgesics and hypnotics. It is also used as an antispasmodic for whooping cough, asthma, hiccup, croup, and related conditions. In various combinations it is indicated for the treatment of hysteria, alcoholic psychoses, etc.

As a sedative:

℞

Chloral Hydrate	4.00 Gm.	(3j)
Sodium Bromide	8.00 Gm.	(3ij)
Hyoscyamus Tincture	8.00 cc.	(f3ij)
Chloroform Water q.s. ad	30.00 cc.	(f℥j)

M. Sig.: Teaspoonful every four hours as required.

Seasickness.—Scopolamine (hyoscine) hydrobromide, 0.00016 gram (1/400 grain), every hour until relief is obtained or overaction appears, has proved to be of value in this condition. Strychnine sulfate, 0.001 gram (1/60 grain), is administered if depression follows its use. The rationale of this therapy cannot be proved, but clinical evidence shows it is effective in many instances.

Paralysis Agitans.—Hyoscine seems to have a selective action on the lower motor centers and is valuable in treating the tremors.

Premedication.—As a preliminary to general anesthesia: Scopolamine and morphine, given hypodermically one-half hour before the general anesthetic, produces a drowsy feeling and lessens the amount of general anesthetic needed, diminishes throat and bronchial secretions, and favors postoperative sleep. Dose: 0.5 mg. (1/120 grain) of scopolamine hydrobromide, and 15 to 30 mg. (¼ to ½ grain) of morphine sulfate. In obstetrics this combination is known as "twilight sleep" because it abolishes the perception and the retention in the memory of the pains of labor. It depresses the respiration of both mother and child and is contraindicated.

Drug Habituation.—Scopolamine is used successfully by some in the treatment of morphine and alcohol addiction.

Urinary Sedative.—One of the most common uses is in the treatment of pain of urethritis and cystitis.

In treatment of cystitis:

℞

Hyoscyamus Tincture	12.00 cc.	(f℥iij)
Potassium Citrate	4.00 Gm.	(℥j)
Distilled Water	120.00 cc.	(f℥iv)

M. Sig.: Teaspoonful in water every three hours.

Frequent urination due to inflammation or irritation of the bladder may be treated by giving 2 cc. of the tincture every hour until relief is obtained, or until toxic symptoms such as flushing of the face and dryness of the pharynx are evidenced.

Preparations

Hyoscyamus, *Hyoscyamus,* U.S.P. Dried leaves with or without tops, yielding not less than 0.04 per cent of alkaloids. *Dosage:* 0.2 Gm. (3 grains).

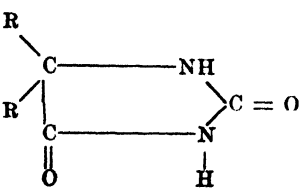
Hyoscyamus Extract, *Extractum Hyoscyami,* N.F. One gram extract represents about 4 grams of hyoscyamus. Yields about 0.15 per cent of alkaloids. *Dosage:* 50 mg. (⅚ grain). *Extractum Hyoscyami Siccum,* B.P. *Dosage:* ¼-1 grain.

Hyoscyamus Tincture, *Tinctura Hyoscyami,* U.S.P., B.P. Hyoscyamus (10%) yields about 0.004 per cent of hyoscyamus alkaloids; in diluted alcohol. Absolute alcohol content about 67 per cent. *Dosage:* 2 cc. (30 minims).

Scopolamine Hydrobromide, *Scopolaminae Hydrobromidum,* U.S.P. The hydrobromide of levorotatory scopolamine. Caution.—Scopolamine Hydrobromide is extremely poisonous. *Dosage:* 0.5 mg. (1/120 grain). *Hyoscinae Hydrobromidum,* B.P. *Dosage:* 1/200-1/100 gr.

HYDANTOIN DERIVATIVES

The hydantoins are built on the formula

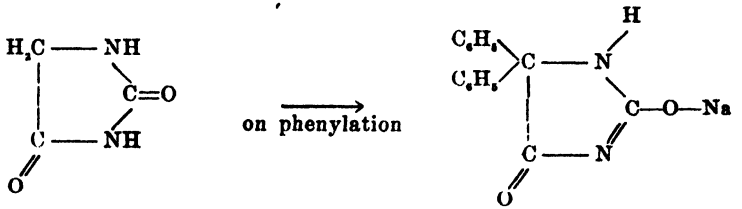


differing from the barbiturates in having an acetic instead of a malonic acid residue. The two important derivatives are diphenyl hydantoin (dilantin) which is used against epileptic convulsions; and phenyl-ethyl hydantoin (nirvanol), which has been used in chorea.

Diphenylhydantoin Sodium (Dilantin)

Diphenylhydantoin Sodium, U.S.P., is sodium 5, 5-diphenyl-hydantoinate, $Na(C_6H_5)_2C.NH.CO:N.C:O$. Dilantin is derived from hydantoin

or prepared synthetically. It is an odorless, white powder with a bitter taste.



Hydantoin Diphenylhydantoin Sodium

Action and Uses.—Diphenylhydantoin sodium is an anticonvulsant and has been found very effective in the treatment of epilepsy. It is more effective in preventing "grand mal" attacks and less effective in the "petit mal" attacks (Merritt and Pitman, 1940). The action is highly selective for the motor cortex. It does not depress other functions of the brain.

Diphenylhydantoin sodium is a valuable drug in the treatment of *epilepsy* because: first, it is superior to phenobarbital in some cases; second, it has no sedative effect in therapeutic doses; and third, it is often a most effective adjunct when used in combination with phenobarbital.

The *dose* varies with the patient, and with the appearance of untoward symptoms. Mild symptoms do not contraindicate the use of the drug. The daily dose for adults is 0.1 Gm. (1½ grains) in a half glass of water three times daily. If necessary this dose may be increased gradually to 0.2 Gm. (3 grains) three times daily. Children above 6 years of age may be given 0.1 Gm. (1½ grains) three times daily for one week, after which the dose may be increased to 0.1 Gm. (1½ grains) four times daily. The drug is more effective if given before meals but may be given after meals if gastric irritation occurs. Children under four years of age may start with 0.03 Gm. (½ grain) mixed with cream (to disguise taste and prevent gastric irritation) twice a day. Increase dose as required.

Toxicology.—Though the anticonvulsant value of diphenylhydantoin sodium is quite striking, its unpleasant side reactions are very prominent. The majority of patients complain of certain troublesome symptoms, the more common of which involve the nervous system. These complaints consisted of tremors and ataxia, a condition which soon passes off. Other complaints are blurring of vision, loss of taste, and dysesthesias in the mouth. Insomnia and irritability were also reported. Less frequent but more serious symptoms were those referable to the skin (toxic dermatitis) and gums (hyperplasia).

N-Methyl, Phenylethylhydantoin

N-methyl, phenylethylhydantoin (mesantoin, phenantoin) has recently been introduced to treat epilepsy, especially grand-mal seizures. It appears to lack some of the toxic manifestations of dilantin. There is evidence, however, that some patients develop tolerance to the drug. Bloom, Lynch, and Brick (1949) reported a case of "mesantoin" poisoning with aplastic anemia and recovery.

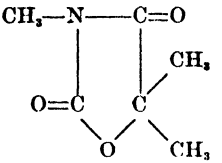
Phenylethylhydantoin

(Nirvanol)

Nirvanol, $C_6H_5C_2H_3C(CONH)_2$, produces marked improvement in some cases of chorea but often causes febrile and exanthematous reactions. Lymphocytosis and eosinophilia usually occur a week or two after the beginning of administration of the drug. This drug is little used now.

TRIMETHADIONE (TRIDIONE)

This substance is 3,5,5,-trimethyloxazolidine-2-4-dione with the following formula:



It possesses hypnotic, analgesic, and anticonvulsant properties. It causes improvement in 83 per cent of patients, and suppresses seizures in 31 per cent. It terminates status epilepticus, but is ineffective against grand mal convulsions. Its mode of action is unknown. The improvement sometimes persists after cessation of treatment (Lennox, 1945). In petit mal epilepsy, the dose required may vary from 1 to 2 Gm. daily, given in divided doses of three to seven 0.3 Gm. capsules per day.

Its toxic symptoms include photophobia, gastric upsets, drowsiness, and light-headedness. Blood changes have been reported following its use. It should be administered under strict supervision until its toxic and therapeutic potentialities are more thoroughly understood. White (1949) reported an incidence of nephrosis occurring during trimethadione therapy.

References

Caffeine and Related Compounds

Huidobro, F., and Amenbar, E.: Effectiveness of Caffeine (1,3,7, trimethylxanthine) Against Fatigue, J. Pharmacol. & Exper. Therap. 84: 82, 1945.

Roth, J. A., Ivy, A. C., and Atkinson, A. J.: Caffeine and "Peptic" Ulcer: Relation of Caffeine and Caffeine-Containing Beverages to the Pathogenesis, Diagnosis and Management of "Peptic" Ulcer, J. A. M. A. 126: 814, 1944.

Strychnine

Aikman, J.: Strychnine Poisoning in Children, J. A. M. A. 95: 1661, 1930.

Anderson, W. F.: The Tonic Action of Strychnine, Brit. M. J. 1: 360, 1944.

Drusser de Barenne, J. G.: The Mode and Site of Action of Strychnine in the Nervous System, Physiol. Rev. 13: 325, 1933.

Travell, J., and Gold, H.: Mechanism of Action of Strychnine on Respiration, J. Pharmacol. & Exper. Therap. 53: 169, 1935.

Picrotoxin, Metrazol, and Nikethamide

Bennett, A. E.: Preventing Traumatic Complications in Convulsive Shock Therapy by Curare, J. A. M. A. 114: 322, 1940.

Ebaugh, F. G.: A Review of the Drastic Shock Therapies in the Treatment of the Psychoses, Ann. Int. Med. **18**: 279, 1943.

Gunther, L.: Engelberg, H., and Strauss, L.: Intramuscular Pressure. II. The Venopressor Mechanism in Shock-like Conditions and the Effects of Various Drugs, Am. J. M. Sc. **204**: 271, 1942.

Hazelton, L. W.: The Present Status of Analeptics, J. Am. Pharm. A. (Scien. Ed.) **33**: 65, 1944.

Lim, K. T., and Snyder, F. F.: The Effect of Respiratory Stimulants in the Newborn Infant, Am. J. Obst. & Gynec. **50**: 146, 1945.

Maloney, A. H., Fitch, R. H., and Tatum, A. L.: Picrotoxin as an Antidote in Acute Poisoning by the Shorter Acting Barbiturates, J. Pharmacol. & Exper. Therap. **41**: 465, 1931.

Anesthetics

Adriani, J.: The Pharmacology of Anesthetic Drugs, Springfield, Ill., 1942, Charles C Thomas.

Beecher, H. K.: The Physiology of Anesthesia, New York, 1938, Oxford University Press.

Carraway, B. N., and Carraway, C. N.: Intravenous Anesthesia, Am. J. Surg. **39**: 576, 1938.

Crossman, L. W., and Allen, F. M.: Surgical Refrigeration and Preservation of Tissue, J. A. M. A. **133**: 377, 1947.

Davison, F. R.: Manual of Toxicology, New York, 1939, Paul B. Hoeber, Inc.

Flagg, P. J.: The Art of Anesthesia, ed. 6, Philadelphia, 1939, J. B. Lippincott Co.

Guedel, A. E.: Inhalation Anesthesia, New York, 1937, The Macmillan Co.

Johnson, Earl: Choice of Anesthesia, Am. J. Surg. **16**: 72, 1932.

Keyes, T. E.: The History of Surgical Anesthesia, New York, 1945, Schuman's.

Lundy, J. S.: Clinical Anesthesia, Philadelphia, 1942, W. B. Saunders Co.

Nosworthy, M. D.: The Theory and Practice of Anesthesia, London, 1935, Hutchinson (Scientific).

Robbins, B. H.: Preanesthetic Medication, Arch. Surg. **40**: 1044, 1940.

Synder, F. F.: Obstetric Analgesia and Anesthesia, Philadelphia, 1948, W. B. Saunders Co.

Weiss, W. A., and Mousel, L. H.: Preoperative and Postoperative Sedation, S. Clin. North America **25**: 1057, 1945.

Curare

Berger, F. N., and Bradley, W.: Muscle-Relaxing Action of Myanesin, Lancet **1**: 97, 1947.

Cullen, S. C.: Curare in Anesthesia, Surgery **18**: 45, 1945.

Gray, T. C., and Halton, J.: A Milestone in Anesthesia (d-tubocurarine chloride), Proc. Roy. Soc. Med. **39**: 400, 1946.

Oxygen

Andrews, A. H., Jr.: Manual of Oxygen Therapy Techniques, Chicago, 1943, Year Book Publisher.

Barach, A. L.: Principles and Practices of Inhalation Therapy, Philadelphia, 1944, J. B. Lippincott Co.

Hypnotics and Sedatives

Bloom, N., Lynch, J. P., and Brick, H.: "Mesantoin" Poisoning With Aplastic Anemia and Recovery, J. A. M. A. **138**: 498, 1949.

DeTakats, Geza: Premedication to Local Anesthesia With Intravenous Barbituric Compounds, Surg., Gynec. & Obst. **50**: 494, 1930.

Everett, G. M., and Richards, R. K.: Comparative Anticonvulsive Action of 3,5,5-trimethyloxazolidine-2,4-dione (tridione), Dilantin and Phenobarbital, J. Pharmacol. & Exper. Therap. **81**: 402, 1944.

Fetterman, J. L.: Dilantin Sodium Therapy in Epilepsy, J. A. M. A. **114**: 396, 1940.

Fisher, J. W.: The Emergency Narcotic Treatment of the Mental Cases, Practitioner **152**: 108, 1944.

Hambourger, W. E.: A Study of the Promiscuous Use of the Barbiturates, J. A. M. A. **112**: 1340-1343, 1939.

Indispensable Use of Narcotics, Chicago, 1931, American Medical Association.

Kozol, H. L.: Epilepsy: Treatment With New Drug: 3-methyl 5, 5-phenyl-ethyl-hydantoin (Phenantoin), Am. J. Psychiat. **103**: 154, 1946.

Kracke, R. R., and Platt, W. R.: Bromide Intoxication From Prolonged Self Medication With B.C. Headache Powder: Report of Two Cases, J. A. M. A. **125**: 107, 1944.

Lennox, W. G.: The Treatment of Epilepsy, M. Clin. North America **29**: 1114, 1945.

Lennox, W. G.: The Petit Mal Epilepsies. Their Treatment With Tridone, J. A. M. A. **129**: 1069, 1945.

New and Nonofficial Remedies, Chicago, 1947, American Medical Association.

Robinson, L. J.: Evaluation of Continued Therapy With Phenytoin Sodium, Am. J. Psychiat. **99**: 231, 1942.

Stern, L., Eisenbud, L., and Klatell, J.: Analysis of Oral Reactions to Dilantinsodium, J. Dent. Research **22**: 157, 1943.

Solomon, M.: Insomnia, M. Clin. North America **29**: 178, 1945.

Tatum, A. L.: The Present Status of the Barbiturate Problem (187 references), Physiol. Rev. **19**: 472, 1939.

Walton, R. P.: Marihuana, Philadelphia, 1938, J. B. Lippincott Co.

White, J. C.: Nephrosis Occurring During Trimethadione Therapy, J. A. M. A. **139**: 376, 1949.

CHAPTER XI

DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM

II. DEPRESSANTS (Cont'd)—ANALGESICS, ANTIPYRETICS, AND ALCOHOLS

ANALGESICS—THE OPIUM ALKALOIDS

Opium is the dried exudation of the *Papaver somniferum*, a poppy which is grown in India, Turkey, Egypt, and Peru. The principal supply in the United States comes from Turkey, largely due to the fact that opium grown in Turkey meets the requirements of the U.S.P. The common red field poppy yields some opium.

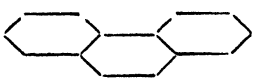
Opium has been used from the earliest times. It was mentioned by Theophrastus in the third century B.C. Galen, a famous physician of the second century A.D., spoke highly of the virtues of opium. Laudanum (tincture of opium) was originated by Paracelsus (1493-1541). Powder of ipecac and opium (Dover's powder) was first compounded and used as a diaphoretic by Thomas Dover, an English physician and pirate, in 1782. Although now much restricted in use, opium is still of great value in medicine.

The active principles of opium were isolated during the first half of the nineteenth century. Morphine, the principal alkaloid of opium, was isolated by Sertürner in 1805; codeine by Robiquet in 1832 and papaverine by Merck in 1848. Crude opium contains twenty or more alkaloids; the most important are:

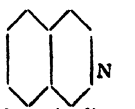
Morphine ($C_{17}H_{19}NO_3$)	10 per cent
Papaverine ($C_{20}H_{21}NO_4$)	1 per cent
Codeine ($C_{18}H_{21}NO_3$)	0.3 per cent
Narcotine ($C_{22}H_{23}NO_7$)	6 per cent
Thebaine ($C_{19}H_{21}NO_3$)	0.3 per cent

MORPHINE

Morphine is a member of the phenanthrene group of alkaloids to which belong the naturally occurring codeine and thebaine and a number of synthetic derivatives including dilaudid and heroin. The isoquinoline group includes narcotine and papaverine as its principal constituents. The predominant action of the phenanthrene alkaloids is on the central nervous system, while that of the narcotine group is on smooth muscle.



Phenanthrene
Morphine
Codeine
Dilaudid
Heroin
Thebaine



Isoquinoline
Narcotine
Papaverine

Pharmacological Action.—The chief actions of morphine are: (1) a depressant effect on the respiratory center; (2) a specific central analgesic action; (3) a descending depressant action on the entire central nervous system; (4) a stimulation of the vomiting center; (5) a constipating effect resulting from central and local actions.

Absorption and Excretion.—Morphine is rapidly *absorbed* following any type of administration except when applied to the skin. It reaches the blood rapidly and remains there about twenty to thirty minutes. It is partially fixed in the skeletal muscles, liver, kidneys, and intestines, and then it is slowly destroyed.

Morphine is *excreted* in the urine, feces, saliva, gastric and intestinal juices. Approximately 10 per cent is excreted in the urine, and a less but variable amount in the feces. The percentage excreted increases but slightly with the dosage. The percentage excretion is not affected by habituation (Frey, 1930). About five-sixths of the total amount ingested is destroyed by the body.

Some of the morphine excreted through the alimentary tract may be reabsorbed into the circulation. Even after hypodermic administration of the drug, it is excreted in part by way of the intestinal tract. Some morphine is said to be excreted in the milk and passes through the placental circulation, often destroying the fetus in utero. The major part of codeine (80 per cent) is excreted in the urine unchanged.

Local Action.—Morphine is practically devoid of local action other than its quieting effect on the intestine. The drug is not absorbed through the intact skin. Morphine and its esters have a direct, mild, irritant skin action, causing erythema which is due to the peripheral vessel dilation. Toxic doses may cause vasoconstriction and blanching.

Action on the Central Nervous System. Action on the Cerebrum.—The action of morphine on the central nervous system in man is mainly depressant, but differs from alcohol and chloroform in its greater action on the respiratory and pain centers. Therapeutic doses (0.008 Gm.) depress the cerebrum. Attention, judgment, and perception are greatly depressed. Imagination is stimulated; this may be due to the removal of normal inhibitions. There is marked effect on pain perception. The pain of disease is deadened or even entirely removed, while intellect remains quite normal. Although constant pain is relieved a sudden blow causes almost as much pain as without morphine; when the patient is aroused, however, the sensitivity to pain becomes more apparent. Morphine seems to lower the power of attention to any constant stimuli. This action may be explained by the special action of morphine on the paths by which pain stimuli reach the consciousness. Morphine is the only drug which acts so specifically on the pain centers, although the antipyrine group of analgesics have a somewhat similar effect.

Small doses of morphine may facilitate certain mental processes and retard others. There may occur a feeling of freedom accompanied by uncontrolled imagination, and these may even be followed by unusual intellectual expression. Just how much of this change is due to increase of mental ability, or just lessened appreciation of distress and worry, is hard to estimate.

The motor areas of the cerebral cortex are not affected by morphine. Because, however, of the increased sensitivity of the cord, the motor areas may appear more sensitive than normal.

Effect on Cerebellum.—Morphine apparently exerts a depressant effect upon the cerebellum, inhibiting motor coordination, rendering the gait of a man clumsy and ataxic.

Effect on Medulla.—Respiratory Center.—The most important effect on the medulla is its depressing action on the respiratory center by lowering its sensitivity to carbon dioxide. Many of the efferent sensory impulses which are essential for the normal functioning of respiration

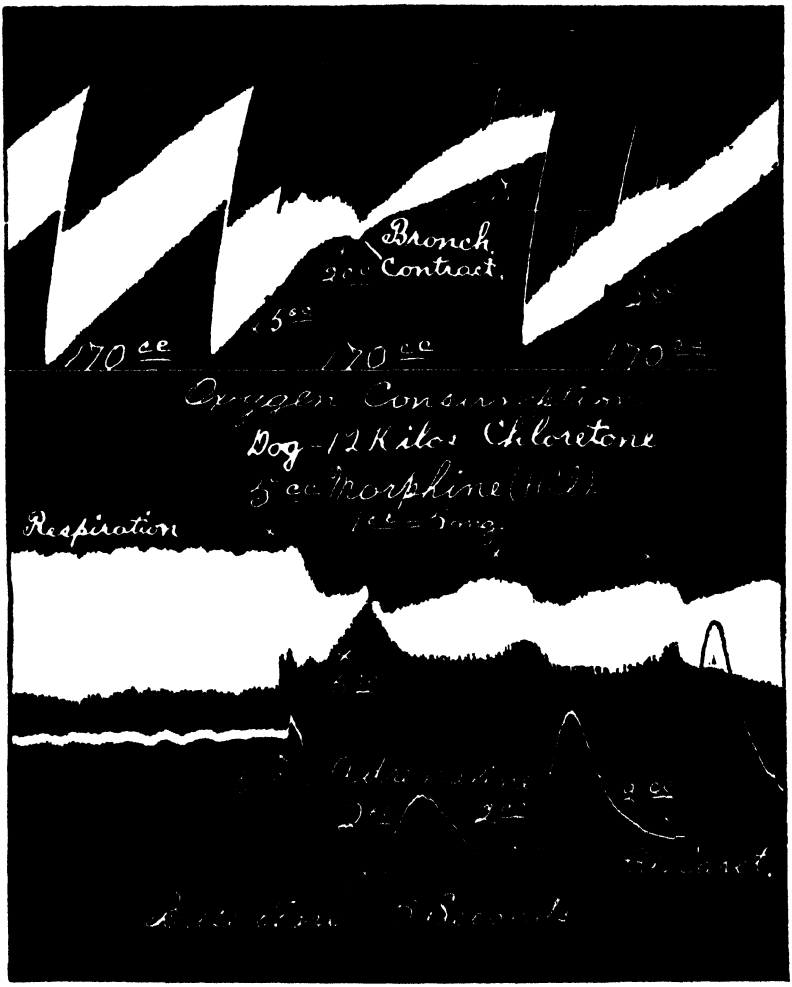


Fig. 4.—Tracing showing the action of morphine (and adrenalin) on the rate of oxygen consumption, on the bronchioles, respiration, and blood pressure in a dog. Note bronchiole constriction and action of adrenalin. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

are cut off by morphine. After small therapeutic doses the breathing becomes shallow, and if sleep follows, the rate of respiration decreases and the depth increases in a slower ratio, so the total air breathed may

fall to approximately one-half the normal. There may follow a Cheyne-Stokes type of respiration. If morphine causes rest and sleep, carbon dioxide is formed in the tissues, and since less is excreted due to slowness of breathing, there may be no accumulation in the blood. The drug therefore deepens the breathing but does not accelerate the rate of respiration.

The mechanism of the slowing of respiration is explained by inattention to the stimuli that normally control it. The response would be less marked to persistent stimuli like carbon dioxide, and more marked toward abrupt stimulation. Morphine causes a constriction of the bronchioles, forcing part of the supplemental or reserve air out of the lungs. Epinephrine counteracts this broncho-constricting action of morphine. (See Fig. 4.) Experimentally it has been shown by Guber at Zurich that animals poisoned by morphine recover if injected with adrenalin. There is also a diminished sensibility to asphyxiation.

Morphine may depress the activity of the *cough* and *heat-regulating centers,* and stimulate the *vasoconstrictor* and *vomiting centers.* These actions are not agreed on by all investigators.

Effect on Pupils.—In man the pupils are constricted by small doses. This action is due to a stronger oculomotor tone, for it disappears when atropine paralyzes the oculomotor endings. This action is central, as it is not produced by local application. The drug, however, may depress inhibitory impulses which keep the oculomotor nerve normal.

Effect on the Spinal Cord.—Morphine and derivatives all increase the spinal reflexes. The effect of morphine on the cord has been studied chiefly in animals. The reflex irritability in frogs is first diminished and then increased. The effect of morphine on the spinal cord is of no therapeutic significance in medicine.

Action on Temperature.—Morphine causes a fall in temperature, partly from diminished movement by which less heat is formed, and partly by loss of heat from peripheral arterial dilatation. Animals under the effect of morphine react sluggishly to any rise in temperature, indicating that the temperature center is less sensitive. It is important to prevent exposure to cold in morphine poisoning. Under morphine poisoning the body temperature may fall two to three degrees.

Effect of Morphine on Circulation.—Therapeutic doses of morphine or its derivatives have little effect on circulation. Following therapeutic doses there is at first a slight acceleration of the heart followed by a moderate slowing, with increased fullness and force. The blood pressure may show a sharp rise, followed by a slight lowering. With toxic doses the fall in blood pressure is marked due to vasomotor depression. The pulse becomes weak and irregular because of disturbed cardiac conduction. The peripheral vessels are dilated by small doses of morphine, causing a redness and flushing of the face.

Action of Morphine on the Alimentary Tract.—The effect of morphine on the intestine varies with the animal. In man morphine produces constipation by diminishing peristalsis and secretions. However, the chief action upon the gut is to produce spasm of the pyloric sphincter and of the ileo-sphincter, thereby delaying passage of the intestinal contents. Because of this quieting effect it is employed in peritonitis and after abdominal operations. This quieting action can be elicited after all the nerves of the stomach and bowels are cut, therefore it is quite independent of the action of the central nervous system. The action may be on the nerve plexus in the intestine. The quieting effect may be attributed to relaxation of the stomach wall or slowing of peristalsis.

Action on Muscles.—In animals many forms of smooth muscles, such as those of the intestine, uterus, ureter, bronchi, and bladder, have shown increased contraction and tone following the administration of morphine and other phenanthrene derivatives, while isoquinoline derivatives apparently depress this activity. Morphine has no specific effect on the uterus but delays labor by its central depression. Large doses are dangerous to both mother and child. Therapeutic doses of morphine relax the bronchial muscles in bronchial spasm, while large doses may produce constriction.

Action on Metabolism.—In man the basal metabolism is decreased by about 25 per cent by 10 to 20 mg. of morphine. Imperfect respiration tends to increase the acid content of the blood and urine and depletes the liver glycogen. Barbour has shown that dogs addicted to morphine have high metabolic rates, which are lowered by withdrawal, and again raised on receiving the drug.

Toxicology.—Opium or its derivatives is frequently employed with suicidal intent or taken by accident. Often after taking the drug the psychic outlook changes and the desire to live encourages the individual to make known the fact that he has taken poison. Opium and morphine exert their toxic actions on the central nervous system, affecting first the higher cerebral centers and then the vital centers of respiration and circulation of the medulla.

Acute Opium or Morphine Poisoning.—This condition may follow oral or hypodermic administration. If morphine is taken orally, symptoms of poisoning appear in twenty to forty-five minutes; if administered by hypodermic, poisoning occurs more rapidly.

The initial symptoms are those of mental stimulation, physical ease, and rapid pulse. These are followed by dizziness, languor, nausea, and a slow and weakened pulse. The pupils become miotic; breathing is slow and accompanied by cyanosis; the lips are livid and the extremities are cold. Respiration becomes Cheyne-Stokes in type and finally death occurs while the patient is in coma.

The *post-mortem* signs are not characteristic. There are visceral congestion and cyanosis. The *fatal dose* varies from one to six grains in non-addicts. Habitués may take as much as 4 grams and show no ill effects. When taken hypodermically, morphine may have three times the effect it exerts when given by mouth. The duration of the acute poisoning is from five to eighteen hours, but may vary from thirty minutes to several days. At *necropsy* of an acute case the materials best suited for analysis are the gastric contents, parenchymatous organs, and the brain.

Treatment.—Early diagnosis is important. The *chief diagnostic symptoms* are coma, pin-point pupils, slow pulse, and characteristic "opium" breath. In more severe cases the breathing is Cheyne-Stokes in type, and the face is cyanotic. In later stages it is almost impossible to arouse the patient. The pupils may become dilated.

Treatment for acute *opium poisoning:* (1) Counteract depression of the respiratory center, (2) prevent pneumonia, (3) heed cardiovascular damage due to opium. The intravenous administration of one or more injections of 5 cc. of the commercial solution of coramine, pyridine-beta-carboxylic acid diethylamide, (25%) to a patient who is comatose due to opium poisoning is often followed by a remarkable improvement. A patient whose respiration is depressed to one or two sighs a minute, who is deeply comatose and cyanotic sometimes wakens up immediately after the first injection.

It is desirable to prevent the development of bronchopneumonia. A good many patients remain drowsy for several hours after the coma has subsided. Therefore add to the routine treatment the intravenous injection of 1 Gm. of sodium sulfadiazine in 20 cc. of water every four hours until the patient can swallow sulfapyridine. Continue this sulfapyridine treatment for at least twenty-four hours after subsiding of coma.

Routine Treatment.—(1) Evacuation of stomach by gastric lavage with several liters of dilute potassium permanganate (1:5000). (2) Administration of an antidote, usually charcoal, a laxative (magnesium sulfate), and high colonic irrigation. (3) Stimulation of heart action by hourly caffeine injections. (4) Every patient with a depression of the respiration below eight per minute should be placed in a Drinker apparatus.

Therapeutic Uses.—Morphine and opium are used mainly to lessen pain, secure sleep, check peristalsis, suppress cough, ease dyspnea, and for premedication. The field of therapy is wide and much discrimination must be exercised in its use.

Opium preparations may be administered internally (in solution or dry form), hypodermically, and by rectum. The preparations frequently used internally in solution are the tincture, the camphorated tincture, morphine sulfate, and codeine sulfate. Powdered opium, powder of ipecac and opium, morphine sulfate, and codeine salts are commonly used in dry form. Morphine sulfate is used hypodermically, the extract of opium is used in suppositories, and the tincture of opium is administered in enemas.

Analgesic.—Morphine surpasses all analgesics, particularly for persistent pain. It is valuable for incurable conditions, such as *inoperable carcinoma*, etc. For these conditions small doses suffice, e.g., 5 to 15 mg. (1/12 to 1/4 grain) hypodermically, repeated if necessary. In relieving the pain caused by fractures, severe burns, renal and hepatic colic, acute inflammation, such as pleuritis, meningitis, etc., morphine has no equal. In surgical conditions in which the alleviation of pain is essential for the success of the operation, small doses of morphine are indicated.

Morphine sulfate, given by vein, is of inestimable value for the prompt relief of the intense agony resulting from a *coronary occlusion*, incidentally lessening the associated shock and quite possibly relieving the regional arterial spasm. Morphine and absolute rest are the best therapeutic measures in *heart block*.

The *technic* employed consists of dissolving 1/4 grain of morphine sulfate in 2 cc. of sterile water and injecting one-quarter of the solution slowly. If, after thirty seconds, no undue reaction is observed, the remainder of the solution is injected slowly.

Full doses of morphine sulfate may be indicated in the beginning of severe cases of *sciatic neuralgia*. In severe cases of dry *pleurisy*, and in *pericarditis*, 0.015 gram (1/4 grain) of morphine sulfate is indicated for pain. Morphine is a valuable sedative in *tetanus* but should not be given in doses large enough to be dangerous. This drug is also indicated in certain cases of *status epilepticus, trigeminal neuralgia, herpes zoster, acute gout, gall-bladder disease, asthma*, etc.

Morphine should not be used for the relief of pain in persons of a neurotic or hysteric temperament, unless its use is absolutely indicated.

Hypnotic.—Morphine may be indicated in insomnia caused by pain, cough, or dyspnea. Small doses of 6 to 8 mg. produce a condition favoring sleep, while larger doses of 15 to 30 mg. compel sleep. In rare instances, where sleep is necessary for recovery, morphine is indicated.

Diarrhea.—Opiates are effective in arresting excessive peristalsis in acute *intestinal catarrh.* It is well to clear the intestines first by a cathartic and then administer ten drops of opium tincture orally. Camphorated tincture of opium and morphine sulfate are commonly used in the intestinal tract.

For diarrhea, dysentery, etc.:

℞

Bismuth Subnitrate	12.00 Gm.	(3iij)
Chloroform Spirit	8.00 cc.	(f3ij)
Camphorated Opium Tincture	12.00 cc.	(f3iij)
Chalk Mixture q.s. ad	90.00 cc.	(f℥iij)

M. Sig.: Teaspoonful in water every fifteen minutes as required.

Cough and Bronchitis.—Opiates check cough by lowering the cough reflex irritability of the respiratory center. It should be remembered that if the cough is "productive," the depression of the cough reflex may lead to a retention of the secretions of the inflamed mucosa. In treatment small doses are indicated, such as 5 mg. of morphine, 10 drops of opium tincture, or 20 mg. of codeine. For children over one year of age 5 mg. of codeine are indicated. Codeine is preferred because there is less tendency to side reactions and habit formation.

For cough:

℞

Codeine Phosphate	0.15 Gm.	(gr.iiss)
Compound Benzoin Tincture	30.00 cc.	(f℥j)

M. Sig.: One teaspoonful every hour.

Child's Cough Remedy (Dr. John Zahorsky):

℞

Glycyrrhiza Fluidextract	120 cc.	(f℥iv)
Ipecac Syrup	100 cc.	(f℥iij)
Compound Opium Tincture	120 cc.	(f℥iv)
Chloroform Spirit	20 cc.	(f3v)
Distilled Water q.s.	1000 cc.	(0ij)

M. Sig.: ½ to 1 teaspoonful every three hours according to age.

In the above formula, the chloroform spirit acts as a local anesthetic for the throat, the paregoric lessens the sensitivity of the cough reflex, the ipecac syrup serves as an expectorant, and the licorice tends to overcome the constipating effect of the paregoric and make the product an excellent vehicle to mask the taste of ammonium chloride or potassium iodide if in certain cases such medication should be found desirable.

Anesthesia.—Premedication.—A small hypodermic dose of morphine (10 mg.) alone or with scopolamine or atropine is usually indicated before administration of general anesthesia. It lessens pain and anxiety and chances of toxic reactions from the general anesthetic.

Scopolamine has synergic effect as a pain depressant, but both scopolamine and atropine antagonize the depressant effect of morphine on the respiratory and vagus centers, antagonizing its stimulating effects upon secretions and upon the vomiting center.

The use of morphine intravenously has been particularly valuable in connection with *spinal anesthesia* when, toward the end of the operation, anesthesia begins to wear off.

In Treating Poisoning.—In case of lead poisoning morphine sulfate, 0.015 gram (¼ grain), and atropine, 0.0006 gram (1/100 grain), are given to relieve colic; the same dose may be used hypodermically to lessen the pain and to secure more cooperation in a patient poisoned by wood alcohol. Morphine sulfate, 0.008 gram (⅛ grain), may be administered in mushroom poisoning to quiet the patient.

Hemorrhage.—Morphine favors the arrest of hemorrhage by quieting the patient and by lowering the blood pressure, thus permitting clot formation. It is indicated in internal hemorrhage, especially pulmonary hemorrhage of tuberculosis. Morphine sulfate, from 0.01 to 0.016 gram (⅙ to ¼ grain), is indicated. Some physicians believe that morphine should never be given to relieve the pain with hemorrhage, because it tends to increase the stasis and hyperchlorhydria that are present in ulcer. It is contraindicated for this use in cardiac or debilatory diseases.

Shock.—Relieve shock by relieving pain. Morphine, ¼ grain or even ½ grain, is used to this end. Morphine is the drug of real value and more lives have been saved by this agent than by all the others together.

Nervous Excitement.—Morphine is indicated in tetanus, delirium tremens, and eclampsia. Administer 10 to 15 mg. hypodermically, every hour, until respiration drops to eight per minute.

Cardiac Asthma.—Morphine is the first drug to be used in cardiac asthma. It may be combined with atropine, but this is not necessary. Reduction of the patient's distress, suppression of the cough reflex, and depression of the respiratory center by morphine often succeeds in terminating the attack. *Dosage:* ¼ grain, subcutaneously repeated at fifteen-minute intervals for four doses if indicated. Dilaudid, grain 1/20, may be used similarly.

Colds.—Colds may be aborted by the diaphoretic action of opium derivatives. Powder of ipecac and opium, 0.5 gram orally, is indicated.

Chronic Opium or Morphine Poisoning (Addiction)

The use of opium has been an important social and medical problem for centuries. Lambert says that peace-loving races use opium, whereas militant races use alcohol, citing China and Japan respectively as examples.

Because of the vigorous enforcement of the Harrison Narcotic Act and treatment of addicts in Federal facilities, the total number of narcotic drug addicts in the United States has declined from 150,000 to 200,000 in 1914 to approximately 48,000 (Vogel, 1949).

The habitués find the effect of the physiological dose pleasant and gradually increase the doses. The continued use causes mental and physical deterioration and predisposes to constipation and intercurrent infections, such as pulmonary tuberculosis, abscesses from subcutaneous injections, and septicemia. There is also a marked deterioration of personality.

Any individual may contract the habit by constant use of the drug. In general, there are two causes of the habit: first, the use of opium in medicine, and second, the initiation of the habit by association. Possibly 50 per cent of the addiction is due to its use in medicine, which imposes on the physician the importance of prescribing opium and its derivatives with the greatest care and secrecy possible to the patients.

The habit usually starts with an individual who is constitutionally unstable emotionally and is subject to feelings of inferiority or has

difficulty in solving his life problems and seeks release by the use of some drug.

Opium may be taken in the form of a powder or as a liquid, by smoking opium, or by the use of opium alkaloids and derivatives, such as morphine and heroin. There is a question as to whether there has been any increase in opium usage in the United States in the last ten years.

Morphine is probably the most common form used in this country. It is usually given hypodermically. Heroin, which is prepared synthetically from codeine, is more stimulating and is largely used by underworld characters. Heroin is used hypodermically or snuffed up and absorbed through the mucous membranes of the nose. Few cases of codeine addiction occur. Some claim that it is not habit-forming.

A high degree of *tolerance* is established in the use of opium and its derivatives. After a period of addiction the patient requires doses that would prove fatal to an average individual. This tolerance also is quickly lost, so that a drug addict, accustomed to the use of 30 grains of morphine, will, after a few weeks of abstinence, be able to tolerate only an ordinary dose. No theory of tolerance is entirely adequate. The different theories include the formation of antibodies in the system, the development of increased ability to destroy the drug, and the development of decreased sensitivity of the cells to the drug.

Tatum suggests the theory that "residues of excitation" are low at the first dose. The patient takes more drug to reduce the excitatory stage leaving thereby greater residues to overcome. Then the addict takes another dose to bring this excitement stage back to normal. Since excitement outlasts depression the addict takes more morphine to overcome the excitement of the previous dose.

Treatment of Opium Addiction.—The complete treatment of addiction comprises two stages: disintoxication and rehabilitation. The former may be accompanied by sudden or gradual withdrawal of the drug, or by withdrawal accompanied by drug substitution. Rehabilitation, or aftertreatment, includes physical rehabilitation and the more difficult problem of mental and emotional stabilization. Psychiatric treatment is usually disappointing because the basic conditions causing the addiction are difficult to correct.

1. *Sudden Withdrawal.*—This is based on the theory that the drug is a poison and that the total suffering from sudden withdrawal is less than the combined suffering of periodic withdrawal. Only young persons are suitable for such treatment.

The patient is placed in an institution, the drug is cut off, elimination is stimulated by cathartics, and the nutrition aided by concentrated diets. Heart stimulants, hydrotherapy, and psychotherapy may be indicated. There are withdrawal symptoms which vary with the individual. The patient usually becomes weak, and has a rapid pulse, followed by restlessness and delirium and frequently collapse.

2. *Gradual Withdrawal.*—The object of this method of treatment is to reduce the drug with the least suffering possible. In recent years, it has rarely been necessary to give more than 30 mg. (½ grain) of morphine every six hours to prevent signs of abstinence during the first two days of withdrawal treatment (Vogel et al., 1948). The same rules of diet, elimination, etc., should be followed.

3. *Drug Substitution.*—This method of withdrawal substitutes some other drug to allay the symptoms of the patient during opium withdrawal. At present, codeine is often substituted with some success. Hyoscine has been used, as has belladonna, a member of the same

family. The Town-Lambert treatment uses the following: "two parts of a 15 per cent tincture of belladonna and one part each of fluidextract of hyoscyamine and xanthoxylum." This mixture is given until symptoms of belladonna poisoning occur.

Sodium amytal is a popular drug for treatment by use of drug substitution. A state of anesthesia is produced over an extended period of time. The use of any drug for long periods will produce ill effects, thus alternation of drugs is advisable.

The United States Public Health Service maintains a narcotic farm at Lexington, Kentucky, where patients may apply for treatment. Convict addicts are treated in the Federal Prison at Leavenworth.

Since the introduction of methadon and its acceptance as a physiologic and psychologic substitute for morphine, the United States Public Health Service Hospital, Lexington, Kentucky, has used it extensively in withdrawing morphine from addicts by shifting to methadon, which is then withdrawn gradually. Usually one can substitute one-fourth the amount of methadon by weight for the dose of morphine the addict has been receiving. Since methadon is a slowly acting cumulative drug, it is started in doses of 10 to 20 mg. (⅙ to ⅓ grain) three times daily twenty-four hours before morphine is discontinued. The dose of methadon is then reduced rapidly over the course of the next ten days.

Preparations

Opium, *Opium*, U.S.P., B.P. Yields not less than 9.5 per cent of anhydrous morphine. *Dosage:* 60 mg. (1 grain).

Powdered Opium, *Opium Pulveratum*, U.S.P., B.P. Contains about 10.25 per cent of anhydrous morphine. *Dosage:* 0.06 Gm. (1 grain).

Ipecac and Opium Powder, *Pulvis Ipecacuanhae et Opii*, N.F., B.P. (Dover's Powder). Powdered opium and ipecac (each 10%) with lactose. *Dosage:* 0.3 Gm. (5 grains).

Opium Tincture, *Tinctura Opii*, Laudanum, U.S.P., B.P. Granulated opium (10%) in alcohol and water. *Dosage:* 0.6 cc. (10 minims).

Camphorated Opium Tincture, *Tinctura Opii Camphorata*, U.S.P. (Paregoric). Opium tincture (4%), camphor (0.4%), benzoic acid and anise oil in diluted alcohol. Absolute alcohol content about 45 per cent. *Dosage:* 4 cc. (1 fluidrachm). B.P. contains 0.05% morphine, etc. 2-4 mils. (30-60 mins.).

Compound Opium and Glycyrrhiza Mixture, *Mistura Opii et Glycyrrhizae Composita*, N.F. (Brown mixture). Comphorated opium tincture (12%), antimony and potassium tartrate (0.024%), with glycyrrhiza fluidextract, glycerin, and ethyl nitrate spirit in distilled water. Absolute alcohol content about 10 per cent. *Dosage:* 4 cc. (1 fluidrachm).

Morphine Sulfate, *Morphinae Sulfas*, U.S.P., B.P. *Dosage:* 10 mg. (⅙ grain).

Morphine Sulfate Tablets, *Tabellae Morphinae Sulfatis*, U.S.P. Usual sizes contain 5 mg., 8 mg., 10 mg., 15 mg., and 30 mg.

Slowly Absorbable Morphine.—A new combination of morphine acetate in a glycerogelatinous base has been used with considerable success. The average time that the effects of such a preparation of the drug can be felt is about sixteen hours with a variation of from ten to twenty hours.

Opium Principles, Derivatives and Allied Drugs

The most important alkaloids extracted from opium and used in medicine are morphine, codeine, and papaverine. The most important derivatives are heroin, dionine, apocodeine, apomorphine, and dilaudid. Isonipecaine and methadon are promising drugs with morphine-like action.

Codeine (methyl morphine) occurs in opium, and is obtained commercially from morphine by methylation. The introduction of the methyl group greatly weakens the narcotic and analgesic effects and intensifies the convulsive properties. Codeine, although less actively analgesic, hypnotic, and sedative than morphine, is preferable if effective, because it is (1) nonhabit-forming, (2) not depressant to respiration in therapeutic doses, and (3) less constipating. The analgesic action is fleeting and large doses are required. Codeine enhances the action of other sedatives and analgesics.

Codeine is especially useful in the following conditions: *In the treatment of cough* morphine is more effective but seldom used because of the danger of addiction. For adults, codeine is especially useful in depressing the cough center. Doses of 15 to 30 mg. (¼ to ½ grain) are indicated for adults.

For acute cough:

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Codeine Sulfate	0.20 Gm.	(f3iij)
Hyoscyamus Tincture	12.00 cc.	(gr.iij)
Tolu Balsam Syrup	90.00 cc.	(f℥ss)
Water q.s. ad	15.00 cc.	(f℥iij)

M. Sig.: One teaspoonful every two hours.

As a mild analgesic in coronary disease, migraine, pericarditis, pleurisy, sciatic neuralgia, etc., codeine, 0.065 gram (1 grain), is usually given. If codeine is not effective, morphine may be indicated.

In the treatment of mild cases of diarrhea administer 60 mg. (1 grain) of codeine phosphate.

In combination with papaverine, codeine is useful in the *treatment of acute colds* (Diehl, 1933). Administer early in order to be effective.

Codeine phosphate may be administered effectively in Glycyrrhiza Syrup, Raspberry Syrup, Wild Cherry Syrup (with glycerin, 25% of total volume).

Codeine is probably more desirable than morphine in the *treatment of asthma.* It controls all but severe paroxysms.

Papaverine.—This drug is an alkaloid obtained from opium and belongs to the benzyl isoquinoline group (that is, it is not a morphine derivative). It stands midway between codeine and morphine in its action on the central nervous system. It does not have the soporific action of morphine nor does it produce the same degree of excitement as codeine. Small doses cause sleep and slow respiration, but this does not become deeper as the dose is increased. The reflex excitability is augmented; large doses may even cause convulsions. Papaverine has been said to lessen peristalsis, but recent investigators disapprove this statement and show that the drug acts much the same on the intestines as does opium.

Combinations of codeine and papaverine were found by Diehl to produce a definite improvement in from 74 to 78 per cent of a large number of cases with *acute coryza, colds, influenza,* and *acute pharyngitis.* The dosage of one-fourth grain of codeine with one-fourth grain of papaverine is recommended. The specific directions for an adult are: one capsule after breakfast, one after lunch, three at bedtime.

Heart Disease.—Papaverine has been recommended for the alleviation of pain in angina pectoris (Katz, 1942) and in the eradication of premature systoles. Because of these two actions and its definite sedative action, papaverine has a definite place in the treatment of chronic coronary disease. It appears to carry none of the hazards of guanidine since it does not depress the heart's contraction. *Dosage:* In severe anginal syndrome give orally 1½ grains three times daily. In premature systoles give 1½ to 3 grains four to five times daily orally.

Papaverine hydrochloride, 0.03 gram (½ grain) intravenously, is useful in the treatment of threatened *gangrene* following the use of ergotamine tartrate. In *pulmonary embolism* administer 50 mg. (¾ grain) of papaverine intravenously.

Papaverine may be given subcutaneously, intramuscularly, or by mouth in doses of 0.03 to 0.13 Gm. (½ to 2 grains). Its toxicity is low.

Narcotine.—Narcotine is another opium drug resembling papaverine rather than morphine, but has even less depressant action. The pulse is slowed by narcotine injection, from direct action on the heart. With narcotine the sympathetic ganglia are first stimulated and then paralyzed, while its action on unstriated muscle is the same as that of papaverine. Narcotine is less toxic than either morphine or codeine.

Thebaine.—Thebaine is still another opium drug that has practically no depressant action. It resembles strychnine but is much less active. It is not used in medicine.

Pantopon.—Pantopon is a preparation of all the alkaloids of opium in the proportion in which they exist in opium. The supposed superiority of the preparation is based on the claim that opium is a better narcotic than morphine, that the impurities are deleted, and that the compound is soluble and may be given hypodermically.

Preparations

Codeine, *Codeina*, N.F., B.P. *Dosage:* 30 mg. (½ grain).

Codeine Phosphate, *Codeinae Phosphas*, U.S.P., B.P. *Dosage:* 0.03 Gm. (½ grain).

Codeine Phosphate Tablets, *Tabellae Codeinae Phosphatis*, U.S.P. Usual sizes contain 15 mg., 30 mg., and 60 mg.

Codeine Sulfate, *Codeinae Sulfas*, U.S.P. *Dosage:* 30 mg. (½ grain).

Codeine Sulfate Tablets, *Tabellae Codeinae Sulfatis*, U.S.P. The usual sizes contain 15 mg., 30 mg., and 60 mg.

Papaverine Hydrochloride, *Papaverinae Hydrochloridum*, U.S.P. *Dosage:* Oral and intravenous 0.1 Gm. (1½ grains).

Morphine Derivatives

Heroin (diacetyl-morphine) is an artificial alkaloid formed from morphine by substituting acetyl for its two hydroxyls. It resembles morphine in its general effects, but acts more strongly on both the cerebrum and medulla, and is therefore more toxic. Heroin has little effect on the intestine. It is thought to be about five times as depressing to respiration as morphine and about thirty times as depressing as codeine.

Heroin is more habit-forming than morphine. The habit is more vicious in every respect. There is rapid mental and moral degeneration. The heroin habit is more difficult to cure, not only in the withdrawal period, but also in the convalescent stage. Relapses are frequent.

Many cases of the heroin habit are on record and this aspect of the drug's action has brought it into disrepute.

Dionin (ethyl morphine hydrochloride, $C_{19}H_{23}O_3N.HCl.2H_2O$). This drug has much the same action as morphine and codeine; in general, its action lies midway between them. It is nonhabit-forming. It is used chiefly in ophthalmology, as an analgesic for ocular pain as found in *iritis, corneal ulcer, scleritis,* and *glaucoma.* When applied to the eye it causes local vasodilatation terminating in acute conjunctival edema. The chemosis thus produced is employed for its analgesic and curative effect. A 2 to 5 per cent solution of dionine is dropped in the eye; following a preliminary irritation of the conjunctiva and cornea lasting about one hour, a period of mild anesthesia results. For relieving a *cough,* ethyl morphine hydrochloride (0.005 to 0.008 Gm.) is very efficient.

Apocodeine ($C_{18}H_{19}NO_2$) is an alkaloid prepared from codeine. It is used in the laboratory to paralyze sympathetic nerve endings and has been suggested as a therapeutic measure for promoting intestinal peristalsis in postoperative conditions. It is contraindicated therapeutically because it is neither efficient nor safe.

Apomorphine is an artificial alkaloid formed by dehydrating morphine through the action of concentrated sulfuric acid. This treatment changes the structure and actions.

$$\underset{\text{Morphine}}{C_{17}H_{19}NO_3}—H_2O=\underset{\text{Apomorphine}}{C_{17}H_{17}NO_2}$$

The narcotic effects of morphine are lost. There results from its use an exciting action on nervous centers, especially the vomiting center. Small doses produce a prompt hypnotic action in acute alcoholism. Large doses cause excitement, convulsions, and death by asphyxia. The emetic action is accompanied by general depression and often by considerable cardiac depression. Apomorphine acts centrally and is the only true central emetic. After hypodermic injection of apomorphine, nausea occurs promptly and vomiting about five minutes later. Smaller doses are expectorant.

Administer 0.006 gram ($\frac{1}{10}$ grain) hypodermically for *emetic* use. Apomorphine is a satisfactory emetic for such conditions as poisoning by arsenic, oxalic acid, wood alcohol, etc.

Dihydromorphinone Hydrochloride (dilaudid) $C_{17}H_{19}O_2N.HCl$ differs essentially from morphine hydrochloride in that one of the hydroxyl groups of the latter has been replaced by a ketone group. Dihydromorphinone hydrochloride is closely allied both chemically and pharmacologically to morphine.

Action and Uses.—Dihydromorphinone hydrochloride appears to have been used satisfactorily in most of the conditions for which morphine is ordinarily used. Its action on the intestine is probably less marked than that of morphine. It is more toxic than morphine but its clinically effective doses are smaller; their therapeutic ratios are approximately the same. It has been shown clinically that dihydromorphinone hydrochloride is powerfully analgesic, and like morphine, it can depress the respiratory center profoundly. Dihydromorphinone hydrochloride has not been proved free from tolerance and addiction properties, and while side reactions seem less frequent than with morphine, the prolonged use should be undertaken with the same caution as with morphine. It comes under the scope of the federal narcotic regulations.

For Relief of Pain in Inoperable Cancer.—Relief was obtained with doses of $\frac{1}{24}$ grain several times daily (Menard, 1933). For moderate

pain dihydromorphinone hydrochloride, 1/48 grain, was satisfactory (Nathanson, 1935).

As an Analgesic in Obstetrics.—Dihydromorphinone hydrochloride gives complete analgesia with apparently less interference with normal labor than morphine. The drug is given in doses of 1/32 grain, or in combination with 1/200 grain of scopolamine. Administer, as with other opiates, after dilatation has definitely begun and the patient complains of severe pains.

In Internal Medicine.—Dihydromorphinone hydrochloride may be administered in 1/20 grain doses for relief of pain in terminal stages of tuberculosis, renal colic, tabetic crisis, cardiac attacks, etc.

For Control of Cough.—Administer 1/66 grain, or less, every three to four hours for control of an irritant cough. For paroxyms give 1/24 grain by injection. Dihydromorphinone hydrochloride may be prescribed with expectorants in the usual opiate-free vehicles.

For coughs:

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Dihydromorphinone Hydrochloride .. 0.03 Gm. (gr.ss)
Terpin Hydrate Elixir ..... 180.00 cc. (f℥vj)

M. Sig.: One teaspoonful every three hours for adults. (For children give smaller doses, 1/128 grain or less.)

PREPARATIONS

Apomorphine Hydrochloride, *Apomorphinae Hydrochloridum*, U.S.P., B.P. *Dosage:* Emetic, hypodermic injection 0.005 Gm. (1/12 grain); expectorant, 0.001 Gm. (1/60 grain).

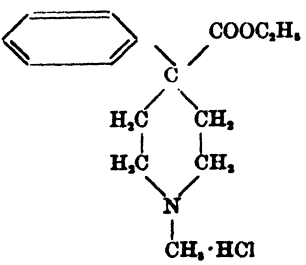
Dihydromorphinone Hydrochloride, *Dihydromorphinoni Hydrochloridum*, U.S.P. *Dosage:* 2 mg. (1/30 grain).

Dihydromorphinone Hydrochloride Tablets, *Tabellae Dihydromorphinoni Hydrochloridi*, U.S.P. Usual sizes contain 1.2 mg. and 4 mg.

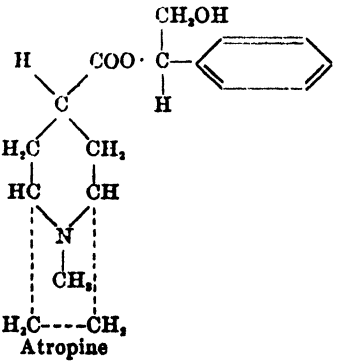
ALLIED DRUGS

Demerol (Meperidine, Isonipecaine)

Demerol (1-methyl 4-phenyl-piperdine 4-carboxylic acid ethyl hydrochloride) was synthesized in 1939 by Eisleb and Schaumann. Its close similarity to atropine can be discerned by inspection of the chemical formulas.



Demerol



Atropine

Action and Uses.—Demerol possesses three main actions: *analgesia, spasmolysis,* and *sedation.* Administered parenterally, demerol is thought to be as effective as morphine in producing clinical analgesia. Comparative studies indicate that 100 mg. of demerol parenterally is equivalent to 10 mg. of morphine. Administration of demerol by the oral route is less satisfactory but yields satisfactory results.

Demerol has definite *spasmolytic action* in man. Clinically this action is manifested by rapid and often dramatic relief of colicky pain. Prolonged use does not result in constipation; hence demerol is of little value in the treatment of diarrhea and cannot replace opiates for this purpose. Several investigators have reported beneficial effects in patients with bronchial asthma. An *acute attack of asthma* can be relieved within ten minutes by the subcutaneous injection of 35 mg. of demerol. The bronchial relaxation is less than that achieved by epinephrine.

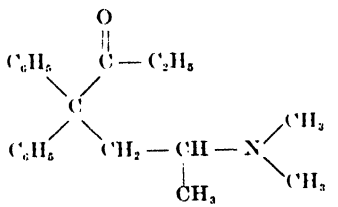
Obstetric Analgesia.—Demerol has recently been used for preanesthetic medication and for obstetric analgesia. It is reported to be superior to morphine since it causes very little respiratory depression, decreases salivation, and does not interfere, to any extent, with pupillary reflex. It is also reported to produce less nausea and vomiting than morphine. Labor may be hastened by its direct relaxing effect on the uterine cervix. If amnesia is also desired, it may be combined with scopolamine or the barbiturates.

Larger parenteral doses of demerol are *sedative.* It produces sleep from which a person can be aroused easily. Its action subsides usually within two hours. It is as satisfactory as a preanesthetic as morphine.

Prolonged use of demerol may lead to the development of habituation, but it appears to possess a lesser tendency in this direction than morphine. In order to avoid any untoward reactions amounts greater than 150 mg. every three hours are contraindicated (Batterman and Himmelsbach, 1943).

Methadon

A recent new synthetic analgesic drug has been introduced. It is the hydrochloride of 1,1-diphenyl-1-(2-dimethylaminopropyl)-2-butanone, also known as methadon, amidone,



The analgesic action of the drug resembles that of morphine; as a preanesthetic agent it is less satisfactory since it causes little euphoria and leaves the patient apprehensive. Methadon causes less gastrointestinal distress and respiratory depression than morphine. Methadon has been used with success as a substitute in withdrawing morphine from addicts (Vogel, 1949). Information on the development, tolerance, and addiction properties of this drug are not available.

Troxil (J. A. M. A. 136: 920, 1948) reported that 10 mg. of *methadon* was as effective as 15 mg. of morphine or 150 mg. of meperidine (demerol). Adequate relief occurred in 81 per cent of 400 patients. Side effects occurred in 13 per cent. Addiction was not definitely established.

ANTIPYRETICS (ANALGESIC ANTIPYRETICS)

Before discussing the antipyretic group of drugs a general discussion of body temperature, factors regulating heat control, and fever will be given.

BODY TEMPERATURE.—The mechanism of the body is adjusted to work at a certain temperature, 37° C. (98.6° F.), which we call normal. Variations from the normal temperature are injurious to the welfare of the body. Surprisingly great diurnal variations are common, usually the difference between morning (36.2° C.) and afternoon (37.5° C.) is greater than 1° C. These variations are dependent upon food, sleep, and change in activity; a brisk walk for two hours may raise the temperature of a healthy person from 37° C. to 38.4° C. These temperatures are reversed by doing night work for a period of years. Mouth temperature is about 0.5° C. below rectal temperature. Body surface temperature may vary according to the region observed.

The limits of temperature within which the brain can function are narrow. A fall of 3° C. below normal produces narcosis, while a rise of 4° C. above normal usually produces delirium.

FACTORS REGULATING HEAT CONTROL.—

1. *Chemical Regulation* (Heat Production).—Chemical regulation of heat is concerned with the formation of heat from food. Surface temperature, type of food, exercise, all play an important part.

The chemical regulation is controlled by the temperature of the sensory nerve ends rather than by that of the environment. A cold environment may add 20 per cent to the metabolic increase. Voluntary and involuntary shivering produce extra heat. Extra heat is also produced without muscular activity, possibly due to the ability of muscle cells to metabolize without movement (Voit).

The chemical substances of certain glands no doubt play some part in the chemical regulation of heat. In cats, using the denervated heart as an indicator, Cannon showed that ice feeding stimulated the adrenal glands; the heartbeat increased after cooling, but not when one adrenal was removed and the other denervated.

Evidence as to whether the thyroid, hypophysis, etc., exert action in chemical regulation is conflicting.

2. *Physical Regulation* (Heat Loss).—Physical regulation takes into consideration heat radiation, conduction, and evaporation of moisture. Radiation and conduction of heat are chiefly controlled by varying rates of blood flow through the skin. Under the effects of cold, the peripheral vessels constrict and blood circulates more abundantly in the viscera; less heat is brought to the surface and lost.

Heat loss by radiation and conduction is at a minimum if the temperature of the environment is at body temperature and from this point evaporation must be depended on for cooling. DuBois found the loss of water from the lungs and skin to be about 700 cc. per day in the normal resting man at 23° C. This is 24 per cent of the water which would have to be evaporated to absorb the total heat lost by the body. The body may form one liter of sweat per hour if necessary.

The amount of heat lost through the various channels in an individual leading a sedentary life in a temperate climate is approximately as follows:

HEAT LOSS	Radiation Conduction	73%
	Evaporation and Sweat	14%
	Respiration	7%
	Warming air and body excretion	6%

3. *Nervous Control of Heat Regulation.*—In general, the higher the central nervous system is developed, the better is the power of temperature control. Cerebral influences are important in heat regulation. Removal of the cerebrum, corpus striatum, and more than the cranial third of the optic thalamus of the dog interferes with heat regulation. Removal of the tuber cinereum destroys it. Destruction of the optic thalamus of pigeons deprived them of heat-regulatory powers (Rogers).

HEAT CENTERS.—The existence of "heat centers" is disputed by some, but there is a temperature center in the sense that certain regions in the floor of the thalamus, when stimulated, will increase the activity of sweat glands. It has also been shown that destruction of these areas markedly interferes with temperature regulation. Cortical influence upon heat regulation is shown by the fact that sleep and narcosis involve some impairment of heat regulation.

Physiology of Fever.—In fever we have to do not only with the direct action of toxins upon the tissues, but also with a disturbance of the heat-regulating mechanism. An excess of heat production is the result, and this is usually accompanied by diminished heat loss. The excess of heat cannot be accounted for by the increase of food intake and therefore must be due to increased metabolic changes, i.e., to increased destruction and accumulation of products of waste in the blood. Thus the disturbance of the heat-regulating mechanism, due to toxins on the center or centers in the brain or cord, leads to a number of secondary disturbances, such as headache, apathy, delirium, etc. All excretions, except that of sweat, are diminished in amount. The skin may be dry, or sweating profusely; in the latter instance, although there is a great loss of heat by the skin, it is still overbalanced by extreme heat formation. The urine is scanty, colored, and often albuminous. There is usually constipation. The flow of saliva is lessened, and the mouth and tongue are dry. The diminished secretion from the trachea and bronchi permit organisms to pass more readily from the mouth to the lungs. Respiration is accelerated due to high temperature in the respiratory center. The heart rate increases and the pulse may be full and bounding, or soft and dicrotic.

The disproportion between heat loss and production accounts for the rigor often present at the beginning of fevers, and for the spasms of cutaneous vessels which produce a sense of cold. The apparent heat of the skin gives no true indication of the internal temperature.

General Treatment of Fever.—The medicinal methods of treatment are:

1. When possible, attack the cause; e.g., use quinine for malaria.
2. Diminish heat production, e.g., *antipyretics.*
3. Increase heat loss, e.g., diaphoretics.
4. Encourage the secretions, e.g., fluids, drugs, etc.
5. Maintain heart strength, e.g., digitalis, strophanthus, etc.
6. Treat symptoms as they arise.

Antipyretics may be applied to diminish heat production. Of these the drugs that do not depress the heart are preferred and should be given only when the fever is high or prolonged. In fever, cold sponging and cold baths are useful. The patient is immersed in the bath at about 40° C., and the temperature of the bath is reduced to 20° C. by adding cold water.

Diaphoretics are used to increase heat loss, e.g., solution of ammonium citrate. Though these may stimulate the action of the skin and increase urine flow, they have little effect on the course of the disease.

The secretory organs may be aided by diminishing the amount of nitrogenous food and substituting milk and cereals. The bowels must be kept open.

The heart strength must be maintained. Digitalis, strophanthus, or strychnine may be indicated. Camphor (10 per cent in olive oil), in doses of 1 to 2 cc., given by muscle, may be used.

It is difficult to outline the treatment necessary, as each case has its peculiarities and complications. In general, a purge, using calomel (3 to 4 grains), followed in four hours by a saline, is indicated.

DRUGS USED TO LOWER BODY TEMPERATURE

Antipyretics are drugs which lower the body temperature, particularly in disease. *Analgesics* are drugs which relieve pain. The antipyretics are of somewhat recent origin. Until 1875 hyperpyrexia was treated by baths and by the administration of such drugs as quinine and aconitine. Buss (1875) discovered that salicylic acid produced a fall in temperature. Somewhat later, phenol and its derivatives were used as antipyretics. Many antipyretics have been introduced and have passed out of use; at present few are used.

The *analgesic antipyretics* or "coal tar analgesics" are benzol derivatives prepared from aniline, a coal tar product. The coal tar analgesics are all white, crystalline powders, and although there are minor differences, they have many characteristics in common. The important antipyretics are acetanilid, phenacetin, phenetidin, antipyrine, and aminopyrine. Some of the derivatives of salicylic acid, such as cinchophen, are sometimes classed with this group of "coal tar analgesics" since they have the same source and produce similar effects.

Pharmacological Action.—The analgesic antipyretics are given orally, and with the exception of aspirin and antipyrine, are rather slowly absorbed. They break down in the body to give the active ingredient *para-aminophenol.* This product is excreted in the urine chiefly combined with sulfuric and glycuronic acids.

The action of antipyretics is evidently that of general depression of the central nervous system. It acts specifically on the heat-regulating center in the corpus striatum and the base of the optic thalamus. The nerve centers are evidently affected, as shown by the relief of pain in neuralgia and headache. Phenacetin causes a lowering of the general sensitiveness of the body, as shown by measuring the threshold of sensibility of the skin. This lowering of the sensibility of the skin is apparent with little depression of mental activity and is therefore quite distinct from analgesia obtained from morphine or anesthetics. This suggests that antipyretics relieve pain by affecting some synapses on the path conveying the pain sensation rather than action on the cerebral cortex. The action may be located also on some "pain center" in the optic thalamus, as antipyretics do not cause somnolence.

During fever the regulatory mechanism is set too high; antipyretics act by depressing the center controlling the temperature. Their action is quite specific on the temperature-regulation center, or at least more strongly active on this center in comparison to its action on other centers.

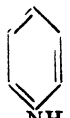
The antipyretic action resides in the benzol ring. Yet benzol (C_6H_6) is not an antipyretic because it cannot react with the body cells; this capacity may be given it by substituting for one of its

H atoms an OH group, as in phenol; or still more strongly by an NH_2 group, as in aniline, or both as in para-aminophenol.

Phenol

Aniline

Acetanilid



Para-aminophenol

Phenetidin

Acetophenetidin

Antipyretics are also analgesics. The mode of analgesic action is not known. They have little action on the vasomotor centers. Antipyretics first accelerate the heart and then slow it by direct action on the cardiac muscle.

Toxicology.—Large doses of "coal tar analgesics" will produce a lowering of body temperature, dyspnea, muscular twitching, mental sluggishness, and collapse. *Treat* by withholding the drug and keeping the patient warm and quiet. Stomach lavage and stimulants are indicated.

Continued use of these drugs impairs the health. Constant use of them may cause rashes, digestive disturbances, palpitation, cyanosis, dyspnea, insomnia and general lowering of body resistance.

Therapeutic Uses.—The "coal tar analgesics" are used to lower body temperature in fever and to relieve all types of pain. They are useful in nervous headache, migraine, neuralgia, etc.

Contraindications.—The "coal tar analgesics" should not be used in treatment of pain due to inflammation, and should not be used by debilitated patients. Certain persons may be sensitive to these drugs and show symptoms, such as skin eruptions, nausea and vomiting, dizziness, cyanosis, and collapse.

Classification of Antipyretics

I. Phenol derivatives.
   - A. Acetanilid.
   - B. Acetophenetidin.

II. Pyrazolon derivatives.
   - A. Antipyrine.
   - B. Aminopyrine (pyramidon).

III. Salicylic acid derivatives.
   - A. Salicylic acid.
   - B. Sodium salicylate.
   - C. Methyl salicylate.
   - D. Acetylsalicylic acid (aspirin).
   - E. Phenyl salicylate (salol).
   - F. Other esters of salicylic acid.

IV. Other antipyretics.
A. Cinchophen.
B. Neocinchophen.
C. Colchicine.

PHENOL DERIVATIVES

Acetanilid — Acetophenetidin (phenacetin)

Acetanilid

Acetanilid is an antipyretic, analgesic, and in excessive doses, a cardiac depressant. It occurs as colorless, shiny crystals or as a white crystalline powder possessing no odor or taste. It is slightly soluble in water (1:190), and freely soluble in alcohol (1:3.4). It is incompatible not only with alkaline bromides and iodides in aqueous solution, but also with chloroform, hydrated chloral, phenol, resorcin, thymol, and spirit of nitrous ether. It has the advantage of cheapness, but its use has been largely abandoned on account of its tendency to produce toxic symptoms.

Pharmacological Action.—Acetanilid readily hydrolyzes into its components; this occurs in the body where aniline is converted into para-aminophenol which is *excreted* combined chiefly with sulfuric and glycuronic acids.

Acetanilid is rapidly *absorbed* from the gastrointestinal tract; it is more rapidly absorbed, however, if given hypodermically. In a normal person 0.5 gram will not affect the temperature, but in fever, such a dose will show effects in two hours and last for three to four hours. The fall in temperature is accompanied by free perspiration and is due to dilation of cutaneous vessels and increased heat loss caused by the action of the drugs on the heat-regulating centers in the brain.

The wide popularity of acetanilid and other coal-tar antipyretics is due almost entirely to their analgesic action on pain due to neuralgia, headache, and rheumatic conditions.

Action on Blood.—The most conspicuous clinical manifestation of chronic acetanilid poisoning is a bluish discoloration of the skin. This has been attributed to the presence of methemoglobinemia by many observers; others claim that para-aminophenol is responsible for the discoloration. Prolonged administration results in the development of *secondary anemia.* The loss of erythrocytes has been attributed to the direct destruction of the red cells by acetanilid or its end-products.

Action on Circulation.—Therapeutic doses of acetanilid have little effect on the heart and circulation. Large doses depress the heart muscle, and death is due to circulatory failure. The cardiac effect in chronic poisoning is partly due to direct action of the drug on the heart muscle and secondarily to the rather marked blood changes.

Toxicology.—Poisoning from acetanilid is mostly accidental, and occurs when the drug is taken indiscriminately for the relief of headaches. A few cases have been suicidal.

The usual action in *acute poisoning* is the production of an intense cyanosis, especially present in the lips which is due to the production of para-aminophenol or possibly methemoglobin. Next, symptoms of weakness, prostration, sweating, feeble pulse and respiration, dyspnea, delirium, convulsions, and death may follow. Death may be due to respiratory paralysis or to toxic action on the heart.

Fatal Dose: Death may result from 5 to 10 grams or more, and may occur in a few hours or in several days. The *postmortem findings* are not characteristic. The *treatment* is to wash out the stomach and give saline cathartics. Stimulants, particularly ammonia and caffeine, may be given. Strychnine may also be of value. Blood transfusions may be necessary. Treat symptoms as they arise. Liver extract and iron are the most important agents in medication.

Chronic Acetanilid Poisoning.—By far the great majority of cases of acetanilid poisoning are of the chronic type. Mild degrees of this condition are common, most cases being attributed to repeated use of the drug in headache and pain-relieving remedies. The continued use has resulted in the development of a genuine craving for acetanilid, with symptoms of great nervousness when use of the drug is stopped. *Symptoms:* Weakness, palpitations, dizziness, loss of appetite, nausea, and occasionally numbness of extremities. The skin may become bluish and the forehead moist with perspiration. The pulse rate is increased. There are signs of cardiac weakness. *Treatment:* Patients with chronic poisoning recover promptly on stopping the drug. Withdrawal of the drug is usually not attended by disagreeable symptoms. If nervousness does occur, sedatives such as the barbiturates may be administered. If a dull pain is present administer acetylsalicylic acid or codeine. Preparations of iron may be given for the associated secondary anemia.

Therapeutic Uses.—This drug is used particularly to relieve headache and neuralgic pain, and the aches and pains of the febrile patient, but is not indicated for the treatment of pain caused by inflammation. It is contraindicated in any form of primary or secondary anemia, advanced cardiac weakness, phthisis or exhausting disease. Many of the so-called "headache powders" contain acetanilid.

For headache (Musser and Kelly: *Practical Treatment):*

℞

Acetanilid	2.25 Gm. (gr.xxxvi)
Citrated Caffeine	0.40 Gm. (gr.vj)
Monobromated Camphor	0.40 Gm. (gr.vj)
Sodium Bicarbonate	1.50 Gm. (gr.xxiv)

M. ft. cap. No. xij.

Sig.: One every hour until three are taken.

For colds (Osborne and Fishbein: *Handbook of Therapy*):

℞

Acetanilid	0.32 Gm. (gr.v)
Sodium Bicarbonate	2.60 Gm. (gr.xl)

M. ft. cht. No. v.

Sig.: One every three hours.

Acetanilid is used in the treatment of *angioneurotic edema* and *urticaria;* give 0.2 gram (3 grains) every two to four hours. Acetanilid is frequently used in severe *dysmenorrhea* to relieve pain; administer 0.2 gram (3 grains). This drug may also prove effective in *migraine;*

administer 0.2 gram (3 grains) with or without caffeine. For the treatment of *whooping cough* acetanilid (0.12 Gm.) and aminopyrine (0.22 Gm.) administered in capsule form are useful.

Acetanilid, being quite insoluble in water, is usually prescribed in capsules or powders. Its indiscriminate use is dangerous. When the Food and Drug Law went into effect (1906) one of the requirements was that if acetanilid was in the remedy this fact, together with the amount, must be stated on the label.

PREPARATION

Acetanilid, *Acetanilidum*, U.S.P. *Dosage:* 0.2 Gm. (3 grains).

Acetophenetidin

Acetophenetidin or phenacetin (proprietary name) is an antipyretic and analgesic employed extensively for the relief of pain. The drug is a colorless glistening crystalline powder, odorless and tasteless; it is very insoluble in water (1:1310) and fairly soluble in alcohol (1:15). It is incompatible with chloral hydrate, iodine, phenol, salicylic acid, and oxidizing agents.

Action and Uses.—Its effects on the system are similar to those of acetanilid, but the poisonous effects are less. This drug is the least toxic of the phenol derivatives. Large doses are toxic to the heart, causing vertigo and some cyanosis, hence the employment of this drug should be most cautious. The indications for its use are the same as for acetanilid. It is *excreted* in the urine as para-aminophenol. Its possible advantage over acetanilid is probably due to the fact that it decomposes more slowly. It exerts a more marked effect on neuralgic pains than do any of the other antipyretics. It is a reliable antipyretic.

The *symptoms and treatment of poisoning* are practically the same as for acetanilid. Skin eruptions are more frequent. Owing to the lack of odor and taste and its limited solubility, it is prescribed almost exclusively in capsules or powders.

For colds (Musser and Kelly: *Practical Treatment*):

℞

Acetophenetidin..... 2.5 Gm. (gr.xxxvj)
Phenyl Salicylate..... 4.0 Gm. (3j)
M. ft. cht. No. xij.
Sig.: One every two hours.

For migraine:

℞

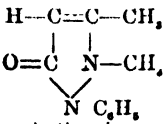
Barbital
Acetophenetidin
Acetylsalicylic Acid.....āā 1.30 Gm. (gr.xx)
M. fiat capsulas No. x.
Sig.: One every two hours as required.

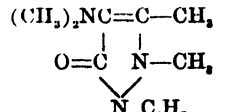
PREPARATIONS

Acetophenetidin, *Acetophenetidinum*, U.S.P. *Dosage:* 0.3 Gm. (5 grains). *Phenacetinum*, B.P., 0.3-0.6 Gm. (5-10 grains).
Acetophenetidin Tablets, *Tabellae Acetophenetidini*, U.S.P. Usual sizes contain 0.12 Gm., 0.2 Gm., and 0.3 Gm.

PYRAZOLON DERIVATIVES

Antipyrine (phenyldimethylpyrazolon) or phenazone is a pyrazolon derivative. *Aminopyrine* (pyramidon) is dimethylamino antipyrine. The formulas are:


Antipyrine


Aminopyrine (pyramidon)

Antipyrine

Antipyrine is a white crystalline powder. It is odorless and stable in air. It is very soluble in water and in alcohol. Antipyrine is incompatible with spirit of ethyl nitrate, nitrites, tannic acid compounds, alkalies, phenol, thymol, etc.

Pharmacological Action.—Antipyrine possesses antipyretic, sedative, and analgesic action. It differs from many other "coal tar" antipyretics in not yielding paraminophenol on decomposition. The drug is rapidly absorbed and appears in the urine either unchanged or in combination with glycuronic or sulfuric acid. Like other coal tar analgesics and antipyretics it probably lessens pain and reduces fever by an action in the subthalamic region of the brain.

It is one of the safest coal tar derivatives, being much less toxic than acetanilid. It has less tendency to cause cyanosis than has acetanilid and apparently does not produce methemoglobin. It has toxic possibilities, however, and should be used with discretion.

Toxicology.—The symptoms of antipyrine poisoning are depression, rapid pulse, collapse, cyanosis, perspiration, and fall in temperature. Convulsions and delirium may occur. Habit formation may result from continued use of antipyrine. The habitual use of the drug leads to (1) digestive disturbances, (2) increased nervousness and insomnia, (3) the production of skin rashes, and (4) chronic poisoning.

Antipyrine poisoning may be *treated* by cleansing with lavage and saline purgatives. Stimulants, such as strychnine, camphor, and ammonia, are indicated. Artificial respiration may be indicated. For chronic poisoning treat symptomatically.

Therapeutic Uses.—It is used for the relief of pain, chiefly of a neuralgic character, and as an antispasmodic in whooping cough. It is not suitable for treatment of pain caused by inflammation.

Antipyrine is generally incompatible; it may, however, be used with caffeine, sodium bromide, and flavored syrups with good results. It may also be prescribed in powders, capsules, or in solution.

Antipyrine may be administered for the *paroxysmal stage of whooping cough.*

Dr. Sauer recommends the following prescription for pertussis (whooping cough):

℞

Codeine Sulfate	0.24 Gm.	(gr.iv)
Antipyrine	2.00 Gm.	(ʒss)
Belladonna Tincture	1.00 cc.	(♏xv)
Saccharin	0.06 Gm.	(gr.i)
Phenobarbital Elixir q.s. ad	120.00 cc.	(f℥iv)

M. Sig.: One teaspoonful every four hours for child.

For hypnotic, analgesic, and antispasmodic:

℞

Codeine Sulfate	0.03 Gm.	(gr.ss)
Antipyrine	1.50 Gm.	(gr.xxiv)
Orange Syrup	60.00 cc.	(f℥ij)

M. Sig.: Teaspoonful every two hours if needed. (For child 2 years old.)

PREPARATION

Antipyrine, *Antipyrina*, N.F. *Dosage:* 0.3 Gm. (5 grains). *Phenazonum*, Antipyrin, B.P., 0.3-06 Gm. (5-10 grains).

Aminopyrine

Aminopyrine or pyramidon is a colorless or white crystalline powder soluble in water (1:18) and in alcohol (1:1.5). It is incompatible with nitrites and tannic-acid-containing preparations.

Action and Uses.—This drug possesses antipyretic and analgesic action, acting somewhat more slowly than antipyrine but with more lasting effect. A single dose may be effective for twenty-four hours. It is *excreted* in the urine, partly unchanged, partly combined with glycuronic acid, and possibly some combined with urea.

It is used alone or with other agents for the relief of headache, neuralgia, migraine, dysmenorrhea, arthritis, neuritis, and related conditions. It is largely used for its synergistic action in combination with opiates and barbituric acid salts. Its *toxic symptoms* and *treatment* are as for antipyrine. The drug is best administered in capsules or in liquids, using aromatic water or aromatic elixir as the vehicle.

Aminopyrine has lately fallen into some disfavor due to its reported etiological relationship to agranulocytosis. The relative frequency with which this occurs indicates that sensitivity probably is a prerequisite to its occurrence. However, it should be administered in small doses and over short periods. Repeated leucocyte and differential counts should be made to guide its use to any great extent. Many proprietary preparations containing aminopyrine are capable of producing primary granulocytopenia. Such a list was published by Kracke and Parker in 1935. There are fifty or more such preparations now on the market.

PREPARATION

Aminopyrine, *Aminopyrina*, U.S.P. *Dosage:* 0.3 Gm. (5 grains). Aminopyrine Tablets, *Tabellae Aminopyrinae*, U.S.P.

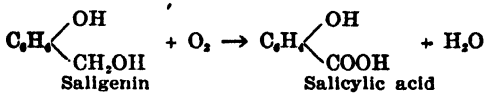
SALICYLIC ACID AND SALICYLATES

The salicylates are among the most useful drugs employed in therapeutics. They were introduced into practice for the treatment of acute articular rheumatism by MacLaglan, of Edinburgh, in 1874. They can hardly be regarded as specific for acute articular rheumatism. If, however, this disease is due to bacteria, and there is every reason to believe that it is, the salicylates would more nearly approach being a "specific" than any of the drugs at our disposal.

The salicylates in the form of decoctions of willow bark were used as a general febrifuge centuries before their true nature was discovered. During the Napoleonic Wars, willow bark was used as a substitute for cinchona bark. The active ingredient of willow bark is the glucoside, salicin, which by hydrolysis yields saligenin (salicyl-alcohol) and glucose.

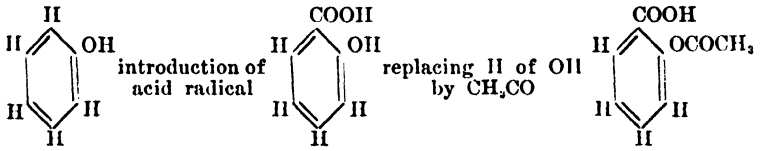
$$\underset{\text{Salicin}}{C_{13}H_{18}O_7} + H_2O \rightarrow \underset{\text{Saligenin}}{C_7H_8O_2} + \underset{\text{Glucose}}{C_6H_{12}O_6}$$

Saligenin on oxidation forms salicylic acid:



Saligenin Salicylic acid

For many years oil of wintergreen was the principal source for obtaining salicylic acid, but with the advent of improved methods of synthesis, salicylic acid is now made synthetically from phenol. Some manufacturers claim that the "natural" salicylates are less toxic and more efficient than the synthetic products. Evidence does not support this claim (Report Council Pharmacy and Chemistry, 1913). The cheaper synthetic product is as effective as the "natural" product (that prepared from oil of wintergreen or birch). Chemically the salicylates are related to the phenols.



Phenol Salicylic acid Acetylsalicylic acid

Salicylic Acid Esters.—To avoid the disagreeable taste and gastric symptoms of salicylates, esters and similar compounds have been made. They are less soluble, so the salicyl radical is liberated in the intestine or after absorption into the blood. Although they have no direct action on the stomach, nausea and vomiting may result from central action. These compounds taste better than the simple salicylates, but they are quite expensive.

Compounds which hydrolyze to produce salicylic acid may include the following types:

1. Simple salts of salicylic acid; e.g., sodium salicylate.
2. Acetyl esters of salicylic acid involving the phenolic hydroxyl group; e.g., acetylsalicylic acid. These derivatives possess a higher analgesic and antipyretic action than simple salicylate salts.
3. Alkyl and aryl esters of salicylic acid involving the carboxylic group; e.g., methyl salicylate and phenyl salicylate, respectively. The alkyl esters (methyl salicylate type) are absorbed readily from the skin and are therefore better for external use than simpler salicylates. The aryl esters (phenyl salicylate type) hydrolyze to active phenols and salicylic acid. They are used but are of doubtful value for intestinal antisepsis.

Pharmacological Action.—Salicylic acid and its derivatives are antirheumatic, diaphoretic, cholagogic, and antiseptic in action. Some also have analgesic, anodyne, and anthelmintic properties.

Salicylates are rapidly *absorbed* from the stomach and duodenum, and circulate in the blood as salicylates of the alkalies. *Excretion* is rapid, and takes place by way of the kidneys, which may be irritated even by therapeutic doses. Excretion begins within fifteen minutes, and is practically completed in six to forty-eight hours. Rapid excretion explains the need for large and frequent doses. The chief product of elimination has been considered salicyluric acid, an inert compound with glycocoll; Hanzlik, however, questions the elimination of salicyluric acid, as only products free of glycocoll are found in the urine. A part is oxidized to dioxybenzoic acid and hydroquinone. Small amounts of salicylates are eliminated with the bile, sweat, and milk.

Salicylic acid has the power of diffusing through skin and this fact places it in a unique position among remedies employed in dermatology.

Action in Rheumatic Fever.—The "specific" action which salicylates produce in cases of rheumatic fever is by far the most important therapeutic action of the drug.

Mechanism of Action on Rheumatism.—The antirheumatic action is probably due in part to the analgesic and antipyretic actions. The salicylates, no doubt, have little germicidal effect in the tissues; nor do they have the disposition to improvement in edemas or irritated tissues. Binz (1879) claimed that carbon dioxide set free salicylic acid from salicylates. He believed that in inflamed joints the high tension of carbon dioxide (17.5%) was sufficient to free salicylic acid, thus producing a local antiseptic of value. Investigators disagree as to the presence of free salicylic acid in joint fluids. Scott, Thoburn, and Hanzlik failed to find free salicylic acid in the joint fluids of rheumatic patients. Much of the comfort derived from the use of salicylates may be due to the depression of the pain centers.

Regardless of mode of action we know:

1. Salicylates do not shorten duration of attack.
2. No antibodies are formed so far as we know.
3. Although salicylic acid is bactericidal in vitro it is doubtful whether it has any such action in the tissues.
4. Salicylates stimulate excretion of uric acid, but they have no material influence on the course of gout. The effect on the uric acid excretion begins at a lower concentration than is necessary to relieve pain in rheumatic fever.

Local Action.—Externally, salicylic acid is an irritant, especially to mucous membranes. Strong solutions of salicylic acid are contraindicated for use in mouth washes, as it tends to soften enamel. Carefully applied to the skin it has the property of softening the epidermis without inducing inflammation. It also tends to arrest local sweating and to promote the growth of normal skin. It has antiseptic action. The salts of salicylic acid also have *antiseptic* action which is much weaker than that of the acid. The liquid salicylates (methyl salicylate) are useful as counterirritants. Internally salicylic acid has the same action as the salicylates.

Analgesic Action.—The pain-reducing action of the salicylates is of great importance in therapeutics because the amelioration or relief of such minor aches and pains as headache, neuralgia, muscular aches and arthralgia forms a large part of medical practice.

Mode of Analgesic Action.—The mechanism of action of salicylate on pain is obscure. Since analgesic doses cause no mental disturbances, no dulling of consciousness, amnesia or change in sensation other than pain sensation, the site of action is evidently not cortical. It is probably due to single depressant action located in the optic thalamus. Some investigators believe that the effect on headache may be due to relief of intracranial pressure by immobilization of excessive water; it may be imagined that something of this kind takes place in the relief of neuralgia. It has also been suggested that these drugs act by producing changes in the meningeal vessels.

Many useful facts relating to *salicylate therapy* have been demonstrated by the studies of Wolff and his co-workers (1941) on the effect of drugs on the pain threshold-raising effect of drugs. Those worthy of special mention are:

1. Maximum analgesic (pain threshold-raising) effect is usually attained with 0.3 Gm. of acetylsalicylic acid.

2. This analgesic action begins in ten to fifteen minutes and reaches its maximum at a point approximately 35 per cent above the control level.

3. The maximum pain threshold-raising effect is secured by 0.3 Gm. of salicylate and lasts from one to one and one-half hours. Larger doses have but a slightly longer analgesic action.

4. Smaller doses at shorter intervals between each administration are more effective in maintaining a high and uniform analgesic action than larger doses administered at longer intervals.

5. The pain threshold-raising effect of acetylsalicylic acid is not raised by codeine, but the combination is useful because of the sedative and hypnotic effects of codeine.

6. The pain threshold-raising actions of acetanilid, acetophenetidin, and aminopyrine are similar. However, acetanilid and acetophenetidin in comparable amounts induce greater relaxation and sedation. Their therapeutic action is undoubtedly to some extent related to their sedative effect.

7. The pain threshold-raising effect of a combination of acetylsalicylic acid, acetophenetidin, and acetanilid is no greater than that of its most effective analgesic agent, acetylsalicylic acid. Sedative effects of the combination, however, are summative.

8. The pain threshold-raising effect of a combination of caffeine citrate, acetophenetidin, and acetylsalicylic acid is no more than that of an equal weight of acetylsalicylic acid, but the sedative effect of the combination seems to be summative.

9. *Preparations containing combinations are rational if they aim to combine pain threshold-raising action with useful sedative and hypnotic effects. However, it is not valid to assume that the pain threshold-raising effects of such combinations are summative.*

Action on Digestive Tract.—Salicylates are irritant to the gastrointestinal tract. Sodium salicylate is less irritating than salicylic acid, but the free acid may be liberated in the stomach by the hydrochloric acid of the gastric juice. Acetylsalicylic acid and phenyl salicylate, however, pass through the stomach without freeing the irritant salicyl group. Salicylic acid arrests fermentation in the stomach and interferes with digestive processes.

Action on Circulation.—Small doses of salicylates may raise blood pressure, chiefly by central vasoconstriction, and such doses also accelerate the heart. Large doses depress the heart by direct action on the cardiac muscle. All doses dilate the skin vessels to some extent. The number of leucocytes may be slightly increased by salicylates.

Antipyretic Action.—Salicylates produce a marked fall in temperature in fever patients. It was originally used as an antipyretic. The antipyretic action is explained on the basis of a dilatation of the cutaneous vessels accompanied by an increase in output of heat. A direct action on the heat centers has not yet been proved. In normal individuals the heat-lowering effect is compensated for by increased heat production, so that no further lowering is attained.

Action on Respiration.—Salicylates cause the respiratory rate to increase and respiratory movements to deepen. Dyspnea may result from direct stimulation of the respiratory center.

Action on Bile Flow.—Salicylates slightly augment bile flow due possibly to some specific action on liver cells. The fluid portion of bile increases in greater proportion than does the organic portion. Salicylates are excreted in the bile and retard bacterial growth. This may be of value in liver and gallbladder infections.

Other Actions.—Salicylates increase nitrogenous metabolism, and also increase the amount of uric acid excreted in the urine. Metabolism is stimulated as shown by an increase of 10 to 12 per cent in nitrogen and sulfur in urine, and by an increase of 30 to 45 per cent uric acid. The alkaline reserve is lowered, producing an acidosis, probably due to an increase in fixed acid. The effects on the central nervous system are slight, except in cases of overdosage and idiosyncrasies.

Toxicology.—Symptoms of mild toxicity are frequent. Serious developments are rare. The common name for salicylate poisoning is *salicylism.* The symptoms of gastric upset are the most common. Nausea, a common symptom, is caused in part by central action and may follow intravenous administration of the drug. A large part of the nausea is due to the liberation of free salicylic acid in the stomach with resultant irritation. This action may be prevented by administration of alkalies. Skin eruptions are fairly frequent, the most common being a scarlatiniform erythema.

Other signs of overdosage are headache, apathy, polyuria, and impairment of hearing and vision. The latter symptoms are due either to local circulatory modification or to degenerative changes induced in the cochlear or retinal nerve cells or in the optic nerve. After very large doses complete deafness or blindness may occur. Very large doses may produce depression of the central nervous system and a slowing of respiration. Large doses are contraindicated in pregnancy, as abortion may result.

In some cases of salicylism, mental excitation ("salicylic jag") is the characteristic feature. The cerebral symptoms simulate those produced by atropine and are talkativeness and great cheerfulness passing on to delirium with hallucinations. Delirium is a common symptom among drunkards who take quantities of salicylates.

The *toxic dose* is approximately 175 grains of sodium salicylate, 120 grains of methyl salicylate, 140 grains of acetyl salicylate. The toxic dose of salicylates is not influenced by age between sixteen and seventy-five years. The toxic dose for children is higher than that calculated for their age. *Treat* by stopping the drug. Bromides are given for cerebral excitement. In the treatment of salicylism, the giving of large doses of sodium bicarbonate has been recommended to hasten elimination of the drug. Vomiting may be relieved by an icebag or mustard plaster over the epigastrium. Treatment should be directed toward maintenance of renal function and the combating of dehydration (Dodd, 1937). Blood transfusions and intravenous dextrose and saline are indicated.

Therapeutic Uses.—*Salicylic Acid.*—Internally it has the same actions as described for the salicylates. Sometimes it is employed in the treatment of rheumatic fever. Locally it is used for the removal of corns, etc.; also to remove the superficial layers of skin, and in the treatment of various skin diseases, such as eczema, dermatitis, and pruritus. It is not often prescribed for internal use, but when so used it is given in capsules. Externally, salicylic acid is used in solution, powder, and ointment.

Salicylates.—The chief use of the salicylates is in the treatment of *acute rheumatism.* The salicylates most frequently used are those of sodium, ammonium, strontium, and methyl salicylate or oil of wintergreen. Those most used at the present time are sodium salicylate and acetylsalicylic acid (aspirin).

Sodium salicylate is the most frequently used preparation. A satisfactory daily dosage is 1 grain per pound of body weight. This is administered in four doses, distributed through the twenty-four hours. Such

dosage may be given for a few days, then reduced as the case warrants it. Administration toward the end of the day may tend to reduce untoward symptoms.

ACUTE RHEUMATIC FEVER.—To effect a cure in rheumatic fever, Coburn (1943) believes one of two objectives must be attained. Either the immune response of the host must be modified so that the patient recovers promptly after his first attack, or the capacity of the infected microorganism to elaborate antigen must be inhibited by the drug used. Since neither of the above objectives has been attained, therapy is limited to suppression of the inflammatory process.

Some investigators believe salicylate therapy may modify the inflammatory reaction and thus inhibit the development of cardiac disease. Reid (1948) concludes that effective treatment of rheumatic fever with salicylate demands that dosage should be controlled by repeated estimations of plasma or urinary salicylate. Coburn believes that a plasma salicylate level of at least 350 micrograms per cubic centimeter may be required to suppress the rheumatic reaction and that plasma level below 200 micrograms per cubic centimeter may be sufficient to relieve symptoms while masking a progressive inflammatory process.

Salicylates promptly relieve all local joint symptoms and fever. Their effects are temporary.

Administration.—1. *Oral Administration.*—Sodium salicylate is used in large doses as a routine measure. Other salicylates, such as acetylsalicylic acid and salysal (salicylic ester of salicylic acid), are effective. There is no evidence that large doses, given routinely, are more beneficial than smaller doses, provided the latter relieves the symptoms. A dose of 1 or 1.5 grams (15 to 22 grains) should be given every three hours for twenty-four hours. If the symptoms are relieved in twenty-four hours the dosage is reduced to 0.7 gram (10 grains) every three to four hours; if sufficient improvement has not occurred, the larger doses are continued until either a beneficial or toxic effect is manifested. These moderate doses are maintained for three or four weeks after symptoms have disappeared and the temperature has become normal. The toxic dose for both sexes is between 8 and 17 grams (120 to 250 grains); the salicylates may be given in flavored solutions (peppermint, etc.) and with bicarbonate, which is supposed to reduce the irritant action on the stomach and kidneys by preventing hydrolysis and checking acidosis. The alkali may be included in the prescription for salicylates or may be taken separately at the same time.

For rheumatic fever:

℞

Sodium Salicylate	15.00 Gm.	(ʒss)
Sodium Bicarbonate	8.00 Gm.	(3ij)
Peppermint Water—q.s. ad	120.00 cc.	(fʒiv)

M. Sig.: Two teaspoonfuls well diluted as directed. Discontinue when ringing in the ears and dizziness develop.

2. *Rectal Administration.*—If salicylates cannot be given orally, they may be given by rectum. After a cleansing enema, about 150 to 250 cc. (5 to 8 ounces) of a thin starch enema containing from 6 to 8 grams (90 to 120 grains) of the salicylate, and from 0.2 to 0.5 cc. (3 to 7 minims) of tincture of opium are given through a rectal tube. A similar dose may be repeated in twelve hours.

3. *Intravenous Administration.*—Pure sodium salicylate, made in 20 per cent solution in sterile distilled water, may be given by vein. The

amount recommended is 3 to 10 cc. of 20 per cent solution. This method is attended by prompt action, and the stomach is protected in most instances. Sterile ampules may be used.

CHRONIC ARTHRITIS.—In the treatment of chronic arthritis salicylates give relief from pain and shorten the course of disease. It is of no value in gonorrheal arthritis or arthritis deformans, and is of little value in gout.

ACUTE TONSILLITIS OR PERITONSILLITIS.—Salicylates are considered of value in relieving pain and swelling in various forms of tonsillitis. Salicylates are given internally. They may be employed also as gargles, using 8 grams of sodium salicylate in 180 cc. of peppermint water (may harm the teeth).

HEADACHES, SCIATICA, ETC.—Acetylsalicylic acid is probably the most frequently used drug for headaches, colds, etc. Bed rest combined with salicylates often is effective in the treatment of *sciatic neuralgia.*

For headache:

℞

Acetylsalicylic Acid ..... 2.00 Gm. (3ss)
Ft. cap. No. vj.
Sig.: One every three hours as required.

PREPARATIONS

Ammonium Salicylate, *Ammonii Salicylas*, N.F. ($NH_4C_7H_5O_3$.) *Dosage:* 1 Gm. (15 grains).

Salicylic Acid, *Acidum Salicylicum*, U.S.P., B.P. Internally it is best given in the form of soluble salicylates.

Sodium Salicylate, *Sodii Salicylas*, U.S.P., B.P. *Dosage:* 1 Gm. (15 grains).

Esters of Salicylic Acid

The introduction of salicyl esters was prompted by a desire to avoid the undesirable taste and the gastric symptoms usually accompanying the use of ordinary salicylates. The esters are more or less insoluble and the salicyl radical is bound so as to be liberated only in the intestine. These compounds apparently act centrally, causing nausea and vomiting. The taste of the esters is more pleasant than that of the ordinary salicylates. The esters have no direct action on the gastric mucosa; sodium salicylate causes no apparent gastric irritation if given with sodium bicarbonate. The most common esters of salicylic acid are acetylsalicylic acid, methyl salicylate, phenyl salicylate and salicin.

Acetylsalicylic Acid (aspirin) is used extensively in place of the salicylates. It was introduced on the theory that it would split up only in the intestines, but it evidently splits up partially in acetic acid and partially in salicylic acid, in both stomach and bowel. The antipyretic action in headache and neuralgia is attributed to the action of acetylsalicylate before it has been decomposed.

It is employed in the medical profession extensively for headache, neuralgia, neuritis, rheumatic fever, chronic arthritis, gout, tonsillitis, influenza, cystitis, etc. It is usually administered with other remedial agents to secure relief from discomforts. It is more easily administered and apparently disturbs the digestive apparatus less than the other salicylates, but it is more depressing.

It is quite insoluble and is best administered in tablets and capsules. As it is an acid, it should not be ordered with alkalies, for this splits

up the drug, liberating salicylic acid which may cause gastric irritation and loss of efficiency of the drug.

The promiscuous use of acetylsalicylic acid (aspirin) by the laity, especially for relief of headache, may lead to poisoning, the chief symptoms being edema of the lips, tongue, eyelids, nose or of the entire face; also urticarial rashes, vertigo, nausea and vomiting and sometimes cyanosis. Allergic persons are especially susceptible to this drug

For rheumatoid arthritis (Russell Cecil):

℞

Acetylsalicylic Acid	0.3 Gm. (gr.v)
Aminopyrine	0.15 Gm. (gr.iiss)
Acetophenetidin	0.15 Gm. (gr.iiss)

M. Sig.: One capsule three times a day.

Methyl salicylate (wintergreen oil, gaultheria oil, sweet birch oil) is antiseptic, antipyretic, antirheumatic, and rubefacient. It is a slightly reddish liquid with an aromatic odor. It is sparingly soluble in water, and miscible with alcohol. When rubbed on the skin it is absorbed, producing mild irritation. When absorbed, or taken orally, it produces the same effects as the salicylates. The absorption is slow and irregular, and overdosage may cause toxic symptoms. It is frequently applied as a counterirritant. It is a frequent constituent of proprietary "balms."

For treatment of neuritis, chilblains, etc.:

℞

Menthol	1.00 Gm. (gr.xv)
Methyl Salicylate	8.00 cc. (f℥ij)
Lanolin	30.00 Gm. (℥j)

M. tere bene.

Sig.: Apply locally as directed.

Phenyl salicylate (salol) possesses antirheumatic, antiseptic, anthelmintic, analgesic, and antipyretic action. Salol was introduced by Nencki in 1886. He sought to avoid the irritant salicylate action on the stomach, to lessen the toxicity, and to obtain a more prolonged salicylate reaction by slow hydrolysis in the intestine. The drug is decomposed only to a slight extent in the mouth and stomach. This drug is a white crystalline powder with a faint aromatic odor and slight taste. It is insoluble in water but soluble in alcohol (1:6). Its antiseptic action is increased when it decomposes into its constituents, phenol and salicylic acid. After absorption it produces the effect of salicylates, but if large doses are administered, phenol poisoning may occur.

Phenyl salicylate is often prescribed alone in capsules, powders, or dissolved in olive oil. No matter how it is given, it frequently nauseates.

For relief of pain in influenza, etc.:

℞

Citrated Caffeine	0.25 Gm. (gr.iv)
Acetophenetidin	1.60 Gm. (gr.xxv)
Phenyl Salicylate	1.60 Gm. (gr.xxv)

M. ft. cht. No. v.

Sig.: One every three hours as required.

Salicin is a glucoside found in willow and poplar bark. This compound may be hydrolyzed into saligenin, which is oxidized to salicylates in the body. Salicin yields 45 per cent of salicylic acid, and is therefore, at the most, one-half as effective. No doubt a decomposition occurs in the intestines similar to that of ordinary esters, for, if given by vein, salicin is excreted unchanged. When given orally it is excreted in the urine partly as salicin, partly as saligenin, and partly as salicylic and salicyluric acids.

Its therapeutic properties, however, have been overlooked. Salicin distresses the stomach much less than aspirin and can be taken over a longer period of time with no ill effects. Being of purely vegetable origin, salicin commends itself over similar drugs of coal tar origin. It is well administered with codeine for treatment of pain in neuritis, and when combined with nux vomica and belladonna it is effective in the treatment of respiratory infections.

Other Esters of Salicylic Acid.—Salysal, N.N.R., salicylic ester of salicylic acid, $HO.C_6H_4COO.C_6H_4COOH$, is insoluble in water and relatively nonirritating. It is approximately twice as active as sodium salicylate and from 5 to 10 grains (0.3 to 0.6 Gm.) two to three times a day is the recommended dosage.

Ethyl Salicylate, N.N.R., the salicylic acid ester of ethyl alcohol, $C_6H_4OHCOO(C_2H_5)$, has the same action as methyl salicylate but is said to be less irritating and less toxic. *Dosage:* From 0.3 to 0.6 cc. (5 to 10 minims) three or four times a day.

Sal-Ethyl Carbonate, N.N.R., $O:C(OC_6H_4.COOC_2H_5)_2$, is antipyretic and analgesic. It is relatively insoluble in water and in the gastric juice, practically avoiding local gastric symptoms and disagreeable taste. *Dosage:* 0.3 to 1 Gm. (5 to 15 grains) three or four times daily as required.

SUMMARY.—In general, methyl salicylate is more efficiently absorbed by the skin and therefore is better for external use. The acetylsalicylates possess higher analgesic and antipyretic actions. Phenyl salicylate is better adapted for use as an intestinal antiseptic. The salicylic esters have no particular advantage over sodium salicylate, but they have the disadvantage of being more expensive.

PREPARATIONS

Acetylsalicylic Acid, *Acidum Acetylsalicylicum,* U.S.P. Aspirin, $C_6H_4.OCOCH_3COOH$. *Dosage:* 0.3 Gm. (5 grains). B.P., 0.3-1 Gm. (5-15 grains).

Acetylsalicylic Acid Tablets, *Tabellae Acidi Acetylsalicylici,* U.S.P. Usual sizes contain 0.06 Gm. and 0.3 Gm.

Methyl Salicylate, *Methyl Salicylas,* U.S.P., B.P. *Dosage:* 0.75 cc. (12 minims).

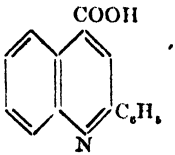
Phenyl Salicylate, *Phenylis Salicylas,* U.S.P. (Salol). *Dosage:* 0.3 Gm. (5 grains).

Salicin, *Salicinum,* N.F. *Dosage:* 1 Gm. (15 grains).

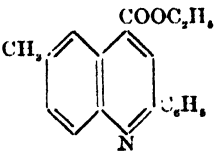
OTHER ANTIPYRETICS

Cinchophen and Neocinchophen

Cinchophen (phenyl-quinoline-carboxylic acid, $C_6H_5.C_9H_4N.COOH$) was introduced under the name atophan, and neocinchophen as novatophan, and while the patents have expired they are still available under these proprietary names.



Cinchophen



Neocinchophen

CINCHOPHEN occurs in small, colorless, needle-like crystals or as a white powder. It is almost insoluble in water but soluble in alcohol (1:120). Neocinchophen is an ethyl-methyl ester of cinchophen which is also insoluble in water.

Pharmacological Action.—Cinchophen and neocinchophen combine the analgesic, antirheumatic, and uric-acid-eliminating properties of salicylic acid with the antipyretic action of quinolin. In gout, the effects of the cinchophens are attributed to increasing the permeability of the kidneys to uric acid and its salts. A single dose exerts its greatest action within three hours and is practically without effect after nine hours. The ability of cinchophen to increase bile flow is more pronounced than that of the salicylates. The renal effects are the same as for the salicyl drugs.

Toxicology.—In recent years a number of cases have been reported in which the use of cinchophens has resulted in liver damage, the most common form being acute yellow atrophy. These drugs certainly are contraindicated in liver disease, and should be administered only under the supervision of physicians, so that jaundice or other evidence of liver injury will be promptly detected. It has been reported that this liver injury followed as small a dose as 37.5 grains of cinchophen. However, Graham (1927) has reported administration of 1.5 grams (22 grains) of cinchophen three times daily for three consecutive days in each week for a period of six and a half years with no apparent injury. Hench (1937), of the Mayo Clinic, says that in view of the slight danger of liver damage balanced against the great relief afforded by cinchophens, one is justified in using them.

Besides hepatic disturbances, other untoward actions of cinchophen and neocinchophen include *cinchonism*, cutaneous eruptions, and gastrointestinal upset. Cinchonism is characterized by headache, tinnitus aurium, deafness, and symptoms of cerebral congestion. The cutaneous manifestations are erythematous rashes, petechiae, pruritus, and urticaria. The gastrointestinal manifestations include anorexia, vomiting, and diarrhea.

Treatment consists in forcing fluids and the administration of glucose in saline intravenously. In *acute poisoning* gastric lavage with potassium permanganate, 1:1000 solution, caffeine and sodium benzoate, 0.5 Gm. (7½ grains) subcutaneously, are of value.

Because of the liver damage cinchophen has been omitted from the U.S.P. Some claim that neocinchophen does not damage the liver.

Therapeutic Uses.—*Cinchophen* has been used rather extensively in the past in the treatment of rheumatic fever, arthritis, gout, neuralgia, etc. Due to the possibility of liver damage it has fallen into disfavor, and its use has been largely abandoned. Beckman expresses his views on their use as follows: ". . . these drugs seem no longer justified in the treatment of rheumatic fever, but it is doubtful whether we can easily spare them in gout; for here the salicylates are by no means so effective."

NEOCINCHOPHEN is employed in the treatment of gout, acute rheumatic fever, neuritis, etc. Although there is a possibility of danger in its use in the treatment of gout, it is still used. It is usually given in tablets or powders. The taste is not disagreeable. Its use should not be continued indefinitely.

Most physicians use 0.5 gram (7½ grains) three times daily during three days a week. This may be continued for a few months at a time.

PREPARATIONS

Neocinchophen, *Neocinchophenum*, U.S.P. *Dosage:* 0.3 Gm. (5 grains).
Neocinchophen Tablets, *Tabellae Neocinchopheni*, U.S.P. Usual sizes contain 0.3 Gm. and 0.5 Gm.
Cinchophen, *Cinchophenum*, N.F. *Dosage:* 0.5 Gm. (8 grains). B.P., 0.3-1 Gm. (5-15 grains).

Colchicine

Colchicine is the active alkaloid obtained from the seeds of colchicum (Meadow saffron) and is thought to have a specific effect on acute gout. It is a pale yellow powder with a bitter taste, and it is insoluble in water but rather soluble in alcohol.

Pharmacological Action.—Colchicine possesses antirheumatic and analgesic action. It is irritant to the skin and causes redness and smarting. When given internally moderate doses have an appreciable effect upon the stomach and intestines, but sometimes its use may cause nausea and vomiting. Small doses are thought to increase the amount of both urea and uric acid eliminated.

Colchicine has the ability to arrest cell division just before its completion. The significance of this is unknown, but it is of interest because of its ability to modify the growth of malignant tumors.

Toxicology.—Overdoses of colchicum produce vomiting, diarrhea, perspiration, heat, and abdominal pain. The pulse becomes rapid and thready. The respiration becomes slow, deep, and finally shallow; death occurs from respiratory paralysis.

Treatment.—Empty stomach by lavage and emetics. Demulcent drinks and tannic acid are indicated. External heat and stimulants may be useful.

Therapeutic Uses.—This drug is employed in the treatment of gout, rheumatic fever, arthritis, and neuralgia. In *gout* give full doses during the attack; this frequently causes nausea and vomiting. Give smaller doses between attacks.

Colchicine is preferable to the wine and tincture of colchicum which often vary in potency and tend to deteriorate. To obtain relief full doses of colchicine must be used: an initial dose of two tablets (each 1/100 to 1/120 grain or 0.65 to 0.63 mg.) followed by one tablet every one or two hours until the pain is relieved and gastrointestinal symptoms (nausea, vomiting, or diarrhea) appear. Then the administration of colchicine should be stopped.

In treatment of gout:

℞

Sodium Salicylate	10.00 Gm.	(℥iiss)
Sodium Bicarbonate	8.00 Gm.	(℥ij)
Colchicum Tincture	15.00 cc.	(f℥ss)
Peppermint Water q.s. ad	120.00 cc.	(f℥iv)

M. Sig.: Tablespoonful every four hours.

PREPARATIONS

Colchicine, *Colchicina*, U.S.P, *Dosage:* 0.5 mg. 1/120 grain). Caution: Colchicine is extremely poisonous (U.S.P.).

Colchicine Tablets, *Tabellae Colchicinae*, U.S.P. The usual size contains 0.5 mg.

Colchicum Seed, *Colchici Semen*, N.F., B.P. Yields not less than 0.45 per cent of colchicine. *Dosage:* 0.2 Gm. (3 grains).

Colchicum Seed Tincture, *Tinctura Colchici Seminis*, N.F. (10% of drug). *Dosage:* 2 cc. (30 minims).

Tincture of Colchicum, *Tinctura Colchici*, B.P. *Dosage:* 0.3-1 mil. (5-15 mins.).

ALCOHOLS

Most alcohols are hydroxy derivatives of the methane series. According to the number of hydroxyls they are classified as: (1) monohydric, i.e., C_nH_nOH; (2) dihydric, etc. No gaseous alcohols are known.

TABLE X

SUBSTANCE	CHEMICAL FORMULA	B.P.	SPEC. GRAV.	RELATIVE TOXICITY (BAER)
Methyl alcohol	CH_3OH	66°	0.812	0.8 (?)
Ethyl alcohol	C_2H_5OH	78°	0.816	1
Propyl alcohol	C_3H_7OH	97°	0.817	2
Butyl alcohol	C_4H_9OH	117°	0.823	3
Amyl alcohol	$C_5H_{11}OH$	131°	0.825	4

The majority of the alcohols are neutral, colorless liquids with a pleasant odor and burning taste. The more important monohydric alcohols, with their formulas, boiling point, specific gravity, and relative toxicity, are listed in Table X.

Ethyl Alcohol

Ethyl alcohol, C_2H_5OH, has been known in an impure form since antiquity. It is obtained by distillation and subsequent purification from fermented mash of potatoes or grain, from fermented sugar, or from wine.

The different alcoholic beverages vary widely in the percentage of alcohol they contain; beers have 2 to 6 per cent; wines 7 to 20 per cent; spirits, such as whisky and brandy, have from 45 to 60 per cent of alcohol by weight. These beverages contain, in addition to ethyl alcohol, higher alcohols of the same series, such as amyl alcohol (fusel oil), and certain etherlike bodies which are slightly more poisonous than alcohol. The toxicity of the various spirits is due chiefly to the ethyl alcohol they contain.

Ethyl alcohol is a colorless liquid of slight odor and burning taste. It is miscible in all proportions with water, chloroform, ether, glycerin, and most oils. It is incompatible with acacia, albumin, bromine, chlorine, chromium trioxide and permanganates. It is solvent for resins, fats, volatile oils and alkaloids. It forms the menstruum in the official tinctures, spirits, elixirs, and most fluidextracts.

Absolute alcohol, i.e., alcohol which is at least 99 per cent pure, occurs as a volatile, inflammable, colorless liquid, with characteristic odor and burning taste. It boils at 77.7° C. It has a marked affinity for water.

Pharmacological Action.—Ethyl alcohol is a local irritant, antiseptic, germicide, diaphoretic, and narcotic. After absorption it depresses the central nervous system, especially the higher centers.

ABSORPTION AND EXCRETION.—Alcohol is one of the few substances which may be absorbed by the blood stream directly from the stomach and the gastrointestinal tract without undergoing digestion. After ordinary amounts are ingested, about 20 per cent is absorbed by the stomach and 80 per cent from the small intestines. After absorption it is distributed to all the body tissues by the circulation. The concentration of alcohol in the blood and body tissues depends on the rate of ingestion of the alcohol, the duration of the time over which this takes place, and the concentration of alcohol in the drink consumed. The liver and brain have a special affinity for alcohol, the liver fixing four times and the brain twice as much as is present in the blood (Pouchet). During or after a meal, much more alcohol can be ingested without toxic effects than can be taken on an empty stomach.

In ordinary amounts, alcohol is almost completely burned up in the body. In larger amounts, not only alcohol, but aldehydes and other incompletely oxidized products of alcohol may appear in the breath and urine. Alcohol never appears in the feces. In the pregnant woman there is the same percentage in the fetal blood as in the mother's blood.

H. W. Haggard and L. A. Greenberg (1934) found that:

"Alcohol is more soluble in urine than in blood; the ratio of distribution at body temperature is of the order of 1 for blood and 1.144 for urine.

"After ingestion of alcohol the concentration in the urine corresponds to that in arterial blood, in accord with the ratio of solubility of alcohol in the two fluids.

"This supports Ambard's contention that alcohol passes through the kidneys by simple diffusion.

"During sixteen hours following ingestion of alcohol, from 2.1 to 4.3 per cent of the total amount is eliminated through the kidneys, the variation depending upon the rate of secretion of urine.

"During a similar length of time about 8 per cent of the total amount of alcohol ingested is eliminated in the expired air. The amount is highly variable, depending upon the volume of respiration.

"The relation of the concentration of alcohol in the alveolar air to that in the arterial blood is exactly that of the distribution of alcohol between air and blood in vitro.

"Contrary to the generally accepted belief, the rate of oxidation of alcohol is not constant regardless of the amount present in the body. On the contrary, the rate of oxidation is proportional to the amount of alcohol present in the body.

"Each hour the amount of alcohol present is diminished by a uniform per cent. In four dogs studied the individual percentage rates ranged from 21.1 to 15.9 with an average of 17.6.

"The solubility of alcohol in the blood is greater than in the tissues as a whole, in the proportion of 1:0.62."

Local Action.—Concentrated alcohol dehydrates and precipitates proteins, which accounts for its irritant and astringent action. Applied to the skin, in a 60 to 90 per cent solution, it produces redness, itching, and burning. In ulcers, unprotected areas, and mucous membranes, the irritant action is very great, being attended by pain and smarting. The astringent and antiseptic actions of 25 to 50 per cent solutions promote healing of ulcers. In the mouth, strong alcohol produces a

burning sensation, and if swallowed, the concentrated vapor may cause an irritation and reflex closure of the glottis.

Subcutaneous injections of alcohol above 50 per cent strength are painful. If injected near a nerve it may paralyze or even destroy it. Eighty per cent alcohol produces immediate and complete paralysis. The paralysis may persist for from one to three years or until nerve regeneration. Varying grades of paresis may be obtained from solutions of alcohol varying in concentration from 25 to 80 per cent strength.

ACTION ON THE CENTRAL NERVOUS SYSTEM.—The chief action of alcohol on the central nervous system, even in small doses, is that of a depressant. Although the early effects suggest primary cerebral stimulation, it is probable that these phenomena result from depression of the inhibitory influence of the higher nervous centers as suggested by Schmiedeberg in 1883 and by the majority of recent observers.

Symptoms resulting from the action of alcohol on the nervous system vary with individuals. One person is rendered sentimental, another bellicose, and a third may show few symptoms. The *symptoms of acute alcoholism* are familiar. Normally the baser tendencies are held in restraint by our higher brain centers. Under alcohol the centers that control reasoning, judgment, self-control, etc., are cut free from restraint. The result is a failure of judgment, failure of moral restraints, speech is freer, and confidence in physical and mental ability rises far above the normal level.

Alcohol in sufficient amounts causes incoordination, characterized by ataxia, inability to use the hands dextrously, and by mixed or incoherent speech. Dodge and Benedict found that small doses caused depression of coordination, as seen in the lowered speed of the eye and various muscular movements. Miles found that for two to four hours after moderate doses of alcohol the patients all had lessened coordination of the eye and hand. Skilled workers performed more slowly and far more errors occurred.

The spinal cord is depressed by alcohol even before signs of cerebral depression occur, as shown by the earlier muscular incoordination and diminished reflex irritability. The simple reflexes in man are lessened in speed and strength by 30 cc. of alcohol. This work was carried out by Dodge and Benedict on the knee jerk and the reflex action of the eyelids. The use of alcohol in large amounts may cause the bladder reflex to fail, resulting in urine accumulation and bladder distention, until catheterization is necessary.

Marchiafava was the first to call attention to alcoholic psychoses and to primary degeneration of the nerve fibers in the corpus callosum and commissure in men. The clinical picture is that of feeble-mindedness and perversion of the moral sense.

ACTION ON RESPIRATION AND CIRCULATION.—The respiratory and circulatory centers function long after there is complete unconsciousness.

Respiration.—There is no unequivocal evidence that the respiratory center is stimulated by small doses (Hyatt). It is well known that in the final stage of acute alcoholic poisoning the breathing becomes more shallow and infrequent, until complete arrest occurs. It requires large doses to depress the center. Alcohol is said to stimulate respiration in shock, but from the practical point of view the question is of little importance, as the stimulation, if present, is too small to be of any therapeutic importance.

Circulation.—There is flushing of the skin in alcohol intoxication due to the dilatation of cutaneous vessels. This is accompanied by a slight constriction of the vessels of the internal organs which causes

a feeling of warmth, but actually heat is lost from the surface, and body temperature falls. Alcohol depresses the heat-regulation center in the same manner as the antipyretics.

Small doses (10 to 25 cc.) in man increase the pulse rate, due chiefly to increased muscular effort and not to direct action on the heart. Excessive amounts of alcohol cause a pronounced fall in blood pressure, since they depress both the heart and vasomotor center, and possibly the vagus.

Blood.—Large amounts of alcohol must be present to cause perceptible changes in the blood in a short time. Small amounts over a long period of time seem to cause an actual mobilization of the lipoids, a lipoidolysis, perhaps the expression of a definite mechanism. In addition, the alkalinity of the blood is lowered, the coagulability increases, and the blood becomes more concentrated.

EFFECTS OF ALCOHOL ON DIGESTION.—Alcohol has an astringent action on the mucous membranes of the mouth and pharynx. There is a brief period of increased flow of saliva. On reaching the stomach, alcohol produces a feeling of warmth and well-being. In small amounts alcohol tends to hasten gastric digestion, but when 5 to 10 per cent alcohol is present, peptic digestion is decreased. It has been suggested that alcoholic polyneuritis and deficiency diseases may be caused in part by faulty digestion and assimilation of food, resulting from the destruction of digestive enzymes by alcohol. Using the Cannon method in the Harvard Laboratory, L. T. Wright found that while a small amount of alcohol mixed with food given to animals accelerated the gastric peristaltic waves and discharge, large doses produced opposite effects, the peristaltic waves being shallow and feeble and the discharge slowed.

It is apparent, from the results obtained from the experiments of various investigators, that sufficient amounts of alcohol inhibit the proteolytic activity of certain gastrointestinal enzymes. When large quantities of liquor are taken over a long period of time, digestive enzymes are destroyed and proper digestion and assimilation of food are prevented. Consequently, a deficiency disease may result.

ACTION OF ALCOHOL ON VARIOUS ORGANS.—The constant use of alcohol causes a gradual degeneration of various organs of the body. The effect is first evidenced by cloudy swelling followed by degeneration of the parenchymatous tissue. This may be followed by connective tissue hypertrophy. These changes are evident in the liver, kidney, and heart. There are other degenerative changes, e.g., fatty degeneration of the intima of the blood vessels. In alcoholics, fatty degeneration of the intima of the blood vessels, with loss of elasticity, and atheroma, with susceptibility to apoplexy, are common (McGuigan, 1940). Chronic catarrh of the stomach, with resulting malnutrition, often results from constant use of alcohol.

THE INFLUENCE OF ALCOHOL ON INFECTION.—Moderate amounts of alcohol increase the susceptibility to bacterial infection. The taking of alcohol day after day for years tends to impair the body structure and decreases the body's resistance to disease. It decreases the processes of immunization and diminishes the power of tissues to heal. There is a high mortality among alcoholics from pneumonia and tuberculosis. Laitinen found by a number of experiments on laboratory animals that those given alcohol showed greater susceptibility to infection and a greater mortality rate than control animals which received no alcohol. He also found it "almost impossible to confer immunity against rabies, tetanus, and anthrax on alcoholized animals."

ALCOHOLIC TOLERANCE.—Repeated doses of alcohol produce a tolerance. This tolerance is due in part to the tissues acquiring an increased capacity to oxidize alcohol and, since oxidation begins at once, a larger quantity is then needed by habitual drinkers to produce intoxication. There is also another factor: the brain will react less to alcohol in the habitual user than in one unaccustomed to the use of it.

THE ANTISEPTIC ACTION OF ALCOHOL.—Alcohol, in 5 to 10 per cent solution, inhibits the growth of bacteria. Dry bacteria may be exposed to absolute alcohol for a long time and survive, while 65 per cent alcohol solution destroys them immediately. This is explained on the greater penetrability of alcohol in the presence of water. Many substances which are antiseptic in water are not effective when dissolved in absolute alcohol because they are not ionized.

THE EFFECT OF ALCOHOL ON GROWTH AND PROGENY.—Stockard found that if male guinea pigs were fed intoxicating doses of alcohol daily for one week and then crossed with normal females, the litters were small and there were many abnormalities; and this effect was transmitted through several generations. There is a tendency in both man and animal for the testes to degenerate under prolonged use of alcohol. The offsprings of habitual drinkers have a tendency to a higher percentage of abnormal progeny. Statistics show that there is a greater proportion of rickets, chorea, tuberculosis, epilepsy, criminality, and alcoholism in the children of alcoholics than in the children of total abstainers. There is no question but that alcohol in the circulation of the mother is capable of causing harm to the child in utero.

Is Alcohol a Food? It has often been claimed that alcohol is of value as a food. It is true that a small amount of alcohol can be burned in the body as starches, fats, and sugars are burned. Alcohol, however, stimulates only normal oxidation. The heat which it liberates is at the expense of the tissues and the oxygen which it utilizes is the oxygen intended to sustain tissue metabolism.

The question of whether alcohol can be considered a food depends on the definition of a food. The following definition is often used: "A food is something essential for the maintenance of life, when taken in the body does not injure it, will supply energy, build up tissues, repair waste, and may be stored in the body." Alcohol is not essential for the maintenance of life, does injure the body, will not build up tissues nor repair waste, and cannot be stored in the body. Alcohol does furnish energy by oxidation and no doubt has a sparing action on carbohydrates and fats.

The food value of alcohol is very limited. Alcohol enters the blood and is oxidized at a constant rate, but the supply of energy is fixed and cannot be adjusted to the needs of the body and cannot be increased to meet a sudden demand. Alcohol cannot be stored for a reserve, nor does it increase the basal metabolism, as is evidenced by ordinary foodstuffs.

Mellanby has calculated that the alcohol oxidized in a dog's body supplied 40 per cent of the total energy lost by the body. He found that the rate of oxidation of alcohol is constant, that about 0.185 cc. of alcohol per kilo per hour is oxidized. He found that this rate was not influenced by concentration of alcohol in the blood or by quantity of alcohol given. He also found that when the metabolism of the dog was increased by severe exercise the rate of alcoholic metabolism was only slightly increased. Higgins measured the respiration quotient in man

and found that when 30 cc. of alcohol were given, oxidation of alcohol began in ten minutes. He found that sucrose and fructose were oxidized with equal rapidity.

Labeling of Alcoholic Beverages.—Much of the damage caused by alcoholism might be prevented if the provisions of the Food, Drug and Cosmetic Act of 1938 were applied to the advertising and sale of alcoholic beverages. The following label in conformity with the Food, Drug and Cosmetic Act of 1938, was proposed by Drs. Alexander, Moore, and Myerson, all of Boston:

"DIRECTIONS FOR USE: Use moderately and not on successive days. Eat well while drinking, and if necessary, supplement food by vitamin tablets while drinking. WARNING: May be habit forming; not for use by children. If this beverage is indulged in immoderately, it may cause intoxication (drunkenness); later, neuralgia and paralysis (neuritis) and serious mental derangement, such as delirium tremens and other curable and incurable mental diseases, as well as kidney and liver damage."

Therapeutic Uses.—During the last one hundred years the use of alcohol in therapeutics has decreased enormously. Pharmacological research during the past forty years has dispelled many illusions concerning the beneficial action of alcohol. The opinion of the medical profession in regard to the value of the internal use of alcohol in therapeutics is divided. It is now recognized, however, that its therapeutic value is limited and its use in the treatment of disease is on the decline.

Externally, alcohol is a *rubefacient* and *astringent*, and by its evaporation, a refrigerant. It is used to harden and cleanse the skin. Soap liniment is used as a mild counterirritant. In a concentration of 70 per cent it is markedly antiseptic and is employed as soft soap liniment in surgery.

Medicated alcohol (about 70%) is frequently employed for giving sponge baths to promote comfort, reduce temperature and prevent bed sores. Alcohol sponge baths are often employed but probably do more harm than good (Bethea).

For excessive sweating of feet:

℞

Alcohol	90.00 cc.	(f℥iij)
Tannic Acid	4.00 Gm.	(3j)
Water q.s. ad	180.00 cc.	(f℥vj)

M. Sig.: Use as wash twice daily.

Alcohol Injections.—Injections of alcohol into or around the vicinity of nerve trunks for the purpose of relieving pain are employed in trifacial *neuralgia* and in *sciatica*. Injections into the superior laryngeal nerve in cases of *laryngeal tuberculosis* have given palliative relief. Alcohol injections are of value in the treatment of *pruritus vulvae*. Several injections are made after anesthesia, using from 2 to 4 minims of 95 per cent alcohol.

Relief of pain in incurable cancer may be secured by injection of a 33 per cent ethyl alcohol solution. This is made of one part alcohol and two parts physiological saline solution. One cc. per Kilo is given every third day. The solution must be administered slowly 30 to 40 drops per minute. The total amount given is increased as the patient's tolerance increases until it reaches between 400 and 600 cc. at one time.

Alcoholism

Recent figures (1948) on the amount spent for alcohol in the United States are of interest. Nine billion, 600 million dollars were spent during the last year. This amounts to $67 for every man, woman and child in the United States or $103 per person over 21 years of age. These figures are three times greater than in 1939. Hence the interest of physicians in the alcohol habit.

There are two forms of alcoholism: (1) the acute type, in which alcoholic poisoning is speedily manifested in active excitement or depression; (2) the chronic type, in which the continued use of alcohol has produced chronic disorders.

Acute Alcoholism.—The toxicologist is usually concerned only with acute alcoholism. The symptoms of acute intoxication in the primary stage are euphoria, exhilaration, soon followed by more advanced emotional symptoms, such as sentimentality or argumentativeness.

Four stages of intoxication are recognized, namely, a *stimulant stage,* characterized by flushing of the skin and excitement; a *narcotic stage* characterized by ataxia and drowsiness; an *anesthetic stage* characterized by stupor; and finally, a *paralytic stage* characterized by slow respiration, slow pulse, dilated pupils, low temperature, and lost reflexes. The patient may recover in a few hours. Often death results from the added strain placed on a preexisting disease, like coronary arteriosclerosis.

Alcohol first acts on the cerebrum, then on the cerebellum, and finally on the spinal cord and medulla. Death results from paralysis of the respiratory center.

The *toxic dose* of alcohol varies from about one to two pints of whisky or brandy (both 45 to 60 per cent alcohol), death usually occurring from five to twelve hours after coma begins. Death usually results when the concentration of alcohol in the blood reaches a concentration of from 0.5 per cent to 1.0 per cent.

The relation between clinical indications of alcoholic intoxication and concentration of alcohol of the blood and urine is presented in Table XI (*Toxicology,* by McNally, 1937).

TREATMENT.—In common drunkenness, provided the respiration is active and the pulse good, the patient should be allowed to sleep. The elimination of the poison occurs rapidly. On awakening, light and easily digested foods are indicated. Ammonium carbonate, 4 grams in a glassful of water, will counteract depression. In severe cases the stomach should be emptied by apomorphine or by a stomach tube. The body temperature should be maintained. Stimulants, such as caffeine, aromatic ammonia spirit, and strychnine, are indicated. As sedatives, paraldehyde and amylene hydrate are often used with good results.

Sodium amytal seems preferable to the old favorite, paraldehyde; but large doses are to be avoided while there is much alcohol in the stomach. Three-tenths gram of sodium amytal every two hours is indicated until the patient becomes drowsy, and thereafter less frequently. When the patient is very disturbed, wet packs, such as a sheet wrung out of cold water and wrapped tightly about the patient, are indicated. Then place over the sheet a heavy blanket tightly tucked in and pinned tightly with large safety pins. The patient may be kept in this pack for three to four hours.

Complications may arise, although they are not common. Pneumonia is not as dangerous as previously, due to the sulfonamide drugs. Dehydration should be cared for. Thiamine hydrochloride is recommended

TABLE XI

STAGE	BLOOD ALCOHOL	URINE ALCOHOL	CLINICAL OBSERVATIONS
Subclinical	0-0.11	0-0.15	Normal by ordinary observation, slight changes detectable by special tests.
Emotional instability	0.09-0.21	0.13-0.29	Decreased inhibitions; emotional instability; slight muscular incoordination; slowing of responses to stimuli.
Confusion	0.18-0.33	0.26-0.45	Disturbance of sensation; decreased pain sense; staggering gait; slurred speech.
Stupor	0.27-0.43	0.36-0.58	Marked decrease in response to stimuli. Muscular incoordination approaching paralysis.
Coma	0.36-0.56	0.48-0.72	Complete unconsciousness; depressed reflexes; subnormal temperature; anesthesia; impairment of circulation; possible death.
Death (uncomplicated)	over 0.44	over 0.60	

according to Jolliffe, in amounts of 20 to 50 mg. daily for three to six weeks. The diet should be liberal and well balanced.

Chronic Alcoholism.—This is a condition resulting from long-continued excessive use of alcohol, characterized by degenerative changes in all tissues, and in addition, inflammatory changes due to local action on the digestive system, which with the nervous system bears the brunt of the attack.

In the digestive system chronic gastritis is frequent. In the earlier stages this is associated with excessive gastric secretion, while later it may progress to the atrophic stage with grave disturbances of digestion and nutrition. Reliable statistics as to the incidence of cirrhosis are not available, but it has been estimated that 5 per cent of all chronic alcoholics have cirrhotic livers and about 50 per cent of all cirrhotic individuals have a history of alcoholic excesses.

The effects of chronic alcoholism on the circulatory system consists of fatty deposits in the myocardium and atheromatous deposits in the large vessels. Some patients develop a persistent tachycardia. The eyes may become watery and bloodshot. Local ecchymosis, acne rosacea, and red face result from continued dilatation of the peripheral vessels. Obesity is a frequent characteristic of this condition.

Chronic alcoholism produces multiple effects on the nervous system. Variable degrees of cellular degeneration combined with demyelinization and atrophy of the convolutions, increase in amount of subarachnoid fluid, and thickening of the meninges are found. Irritability, forgetfulness, impairment of judgment, unsteady motions and tremors are characteristic findings. Expressions of more severe deterioration are *delirium tremens, alcoholic wet brain,* and *Korsakoff syndrome.*

Delirium tremens is an acute metabolic and psychological disturbance occurring in drunkards. It may be precipitated by a debauch, sudden withdrawal of alcohol, trauma, hemorrhage, operations or acute infections, especially pneumonia. The onset may be sudden or the attack may be preceded by restlessness, insomnia and tremors. The characteristic symptoms are tremor, delirium and albuminuria. The delirium is a hallucinatory confusion, visual and auditory. In severe cases the mortality is high. Fever and acidosis are usually present. The terminal stage is usually ushered in by an abrupt rise in temperature to 103° to 105°.

The *alcoholic wet brain* is a grave condition which occurs in chronic alcoholics who have usually had preceding mental disturbances. Confusion passes into stupor or coma. Fever is a characteristic finding. No consistent pathological findings are present. The mortality is high.

Korsakoff syndrome or psychosis polyneuritica, is characterized by loss of memory, tremors, thick speech, visual hallucinations, associated with polyneuritis (vitamin B_1 deficiency). Other mental disturbances include chronic hallucinosis and states which simulate paranoid dementia.

Treatment.—Prognosis is poor. Dementia is permanent. There are no specifics or combinations of drugs that can effectively check the drink impulse except at the peril of its breaking out again with greater force. Institutional therapy offers the best immediate hope. Effective treatment should include the substitution of other interests for the emotional appeasement received from alcohol. Withdrawal of alcohol, medication with the barbiturates and with scopolamine, and frequent saline cathartics form the basis of treatment of chronic alcoholism. Amphetamine (benzedrine) sulfate has been found useful in the treatment of alcoholism. Bloomberg (1939) recommends 20 mg. daily in divided doses to alleviate the craving and thus enable the patient to become re-established.

In the treatment of chronic alcoholism two other methods deserve brief mention because of the success they have attained—namely *Alcoholics Anonymous* and the other, the *conditioned reflex* treatment.

Alcoholics Anonymous is a psychological approach to the problem. Dr. P. L. Smith in *Psychiatric Quarterly* (Official Organ of New York Department of Mental Hygiene) reported 50.1 per cent recovery in a group of 111 patients.

Conditioned Reflex Treatment. This method is based on the establishment of an unpleasant conditioned reflex to accompany the drinking of alcoholic beverages. The patient is given a dose of emetine hydrochloride (about 1 grain) with his favorite drink. This leads to nausea, and when this appears a further dose of emetine hydrochloride is injected, which causes vomiting in two to eight minutes. By repeating this procedure several times on different occasions the patient then finds that he becomes nauseated and vomits when he takes a drink which does not contain emetine.

Dr. H. Reese uses this method in Madison, Wisconsin, on chronic alcoholics who appear in court and wish to be cured; they are detained for thirty days. He regards this method as the only effective method of treating alcoholics.

For delirium tremens and alcoholic wet brain injections of hypertonic solutions, alkalinization, and circulatory stimulants are indicated. Recently, 5 per cent glucose solutions and salt tablets have been used successfully in delirium tremens. Frequent drainage of spinal fluid may be indicated to relieve its increased pressure. Paraldehyde or

sodium amytal are indicated for maniacal symptoms. Intravenous injections of vitamin B_1 (50 mg) daily for several days have been recently recommended.

PREPARATIONS

Alcohol, *Alcohol*, U.S.P., B.P. Not less than 92.3 per cent by weight and 94.9 per cent by volume C_2H_5OH.
Dehydrated Alcohol, *Alcohol Dehydratum*, N.F., B.P. ("Absolute Alcohol") 99% by wt. C_2H_5OH.
Diluted Alcohol, *Alcohol Dilutum*, U.S.P. 49% by vol. C_2H_5OH.
Whisky, *Spiritus Frumenti*, U.S.P. 50%. C_2H_5OH.
Brandy, *Spiritus Vini Vitis*, U.S.P. 51%. C_2H_5OH.

Methyl Alcohol

Methyl alcohol (methanol), CH_3OH, is contained in methylated spirit (5 to 10 per cent) and is the chief constituent of wood spirit. It is not employed as a therapeutic agent, but is of interest chiefly from the toxicological standpoint.

Action and Uses.—In general, the action of methyl alcohol is similar to that of ethyl alcohol and is exerted mainly on the central nervous system. The drug is slowly destroyed in the body and its cumulative action is a result in part of its slow excretion. After giving approximately 120 cc. Voeltz and Dietrich (1912) found that during twenty-one days about 21 per cent was excreted unchanged by the lungs, 3 per cent in the urine, 39 per cent was burned, and 37 per cent still remained in the tissues.

Methyl alcohol is used extensively in various industries. Among the common uses are: as a solvent for shellac, in paints and varnishes, as radiator antifreeze, as an adulterant of alcoholic beverages, in cosmetics, and in a number of other industrial processes.

Toxicology.—Methyl alcohol is especially an American poison and has probably done more damage in the United States than in all other civilized countries put together (Hamilton).

The symptoms of acute methyl alcohol poisoning are very similar to those of ethyl alcohol poisoning so far as the intoxication is concerned, but differ in that in methyl alcohol toxicity there is marked irritation and the after effects are more serious. This may be partly explained by the difference in oxidation of methyl alcohol in the body. Ethyl alcohol is oxidized to carbon dioxide and water, while methyl alcohol, on the other hand, is oxidized very slowly to formaldehyde and formic acid, both of which are intensely irritating.

The initial symptoms of poisoning occur rapidly; they are abdominal pain, general weakness, nausea, vomiting, headache, cramps, dyspnea, and cyanosis. If recovery does not occur, there is marked depression of the heart, a sighing respiration, cold sweats, delirium, coma, and death. Blindness may appear in a few hours or be delayed.

One of the sequelae of methyl alcohol poisoning is bilateral impairment of vision. This may occur in acute attacks or follow chronic exposure to the drug. The symptoms appear early or after a few days, with photophobia, followed by gradual loss of sight due to atrophy of the optic nerves.

The *fatal dose* varies from 30 to 60 cc. The patient may die in from twenty-four hours to three days. At *autopsy*, the skin is cyanotic and the organs are congested, especially the brain. The lungs are usually edematous.

TREATMENT.—If the patient is seen within twelve hours of ingestion of alcohol and is not comatose, the stomach should be washed out with a warm 2 per cent solution of sodium bicarbonate, followed by a 50 per cent solution of magnesium sulfate. Warmth is essential. Follow every two hours with 3 Gm. of sodium bicarbonate in a glassful of water until several doses have been given. If there are coma, cyanosis, and depressed circulation, administer intravenously 1,000 cc. of Fischer's solution (0.37 per cent sodium carbonate, and 1.4 per cent sodium chloride).

Isopropyl Alcohol

Isopropyl alcohol, Propan-2-ol.$CH_3.CH(OH).CH_3$, is a clear, colorless liquid with characteristic odor and a bitter taste. It is miscible with water in all proportions and is miscible with chloroform and ether, but insoluble in salt solutions. Its specific gravity at 25° C. is from 0.780 to 0.790. It volatizes at low temperature and boils at from 81° to 82° C.

Isopropyl alcohol is a solvent for creosote and may be used as a *prophylactic agent against creosote burns.* Recent investigations indicate that isopropyl alcohol compares favorably with ethyl alcohol in *anti-infective action.* It has been ranked ahead of ethyl alcohol as a disinfectant for the hands. It has been recommended for the *disinfection of the skin* and of hypodermic syringes and needles. A 50 per cent solution colored red is used for preoperative preparation by the surgeon and also on the field of operation. Since it does not affect the potency of insulin, it can be used as a distinfecting agent in connection with the administration of this drug.

Isopropyl alcohol is suitable for *rubbing compounds,* the following formula having been used for the University Hospital of the University of Michigan, as a back lotion.

R

Isopropyl Alcohol	25.0 cc.
Glycerin	10.0 cc.
Acetic Acid, 4 per cent	2.5 cc.
Water, q.s.	100.0 cc.

Coloring and perfume may be added.
M. Sig.: Use as rubbing compound.

References

Opium Alkaloids and Derivatives

Andrews, H. L., and Himmelsbach, C. K.: Relation of the Intensity of Morphine Abstinence to Dosage, J. Pharmacol. & Exper. Therap. 81: 288, 1944.

Batterman, R. C., and Himmelsbach, C. K.: Demerol: A New Synthetic Analgesic (35 References), J. A. M. A. 122: 222 (May 22), 1943.

Davison, F. R.: Manual of Toxicology, New York, 1939, Paul B. Hoeber, Inc.

DeLee, J. B.: Indispensable Uses of Narcotic Drugs in Obstetrics and Gynecology, J. A. M. A. 96: 1007, 1931.

Himmelsbach, C. K.: Studies of the Addiction Liability of "Demerol" (D-140), J. Pharmacol. & Exper. Therap. 75: 64, 1942.

Krueger, H. M.: Action of Morphine on Digestive Tract, Physiol. Rev. 17: 618-645, 1937.

Krueger, H., Eddy, N. B., and Sumwalt, M.: The Pharmacology of the Opium Alkaloids, Parts 1 and 2. Supplement No. 165 to the Public Health Reports, U. S. Public Health Service, Federal Security Agency, 1941, 1943.

Literature on the opium problem up to 1928. The Opium Problem by Terry, Charles E., and Pellens, Mildred, for the Committee on Drug Addiction, in collaboration with the Bureau of Social Hygiene, Inc., New York.

Pfeffer, A. Z.: Psychosis During Withdrawal of Morphine, Arch. Neurol. & Psychiat. **58**: 221, 1947.

Scott, C. L.: The Morphine Habit, London, 1937, H. K. Lewis & Co.

Scott, C. C., Kohlstaedt, K. G., and Chen, K. K.: Comparison of the Pharmacologic Properties of Some New Analgesic Substances, Anesth. & Analg. **26**: 12, 1947.

Small, L. F.: Chemistry of the Opium Alkaloids, Pub. Health Rep. Supplement, Bull. No. 103, 1932.

Slaughter, D.: New Concepts of Morphine Analgesia, Anesthesiology **5**: 508, 1944.

Tatum, A. L., and Seevers, M. H.: Theories of Drug Addiction, Physiol. Rev. **11**: 107, 1931.

Vogel, V. H., Isabell, H., and Chapman, K. W.: Present Status of Narcotic Addiction, J. A. M. A. **138**: 1019, 1948.

Yonkman, F. F., Noth, P. H., and Hecht, H. H.: Demerol: a New Synthetic Analgesic, Spasmolytic and Sedative Agent, 1, Pharmacologic Studies, Ann. Int. Med. **21**: 7, 1944.

Antipyretics

Barbour, H. J.: The Heat-Regulating Mechanism of the Body, Physiol. Rev. **1**: 295, 1921.

Bartels, E. C.: Successful Treatment of Gout, Ann. Int. Med. **18**: 21, 1943.

Bauer, W., and Klemperer, F.: The Treatment of Gout, New England J. Med. **231**: 681, 1944.

Coburn, A. F.: Salicylate Therapy in Rheumatic Fever, Bull. Johns Hopkins Hosp. **73**: 435, 1943.

Dilling, W. J.: Modern Therapeutics, VIII, Sedatives and Analgesics, Practitioner **144**: 189, 1940.

Dubois, E. F.: The Mechanism of Heat Loss and Temperature Regulation, Ann. Int. Med. **12**: 388, 1928.

Gross, M.: Acetanilid; a Critical Bibliographic Review, New Haven, 1946, Hillhouse Press.

Kracke, R. R.: Relation of Drug Therapy to Neutropenic States, J. A. M. A. **111**: 1255, 1938.

Livingston, W. K.: Pain Mechanisms, New York, 1943, The Macmillan Co.

Reid, J.: Does Sodium Salicylate Cure Rheumatic Fever? Quart. J. Med. **17**: 139, 1948.

Sable, H. Z.: Toxic Reactions Following Salicylate Therapy, Canad. M. A. J. **52**: 153, 1945.

Wolff, H. G., Hardy, J. D., and Goodell, H.: Studies on Pain, J. Clin. Investigation **18**: 648, 1940; **20**: 63, 1941.

Wooley, V. J.: Modern Therapeutics, XIV, Antipyretics, Practitioner **145**: 132, 1940.

Alcohols

Archer, G. T. L.: Bactericidal Effect of Mixtures of Ethyl Alcohol and Water With Special Reference to Sterilization of the Skin, and a Note on the Comparable Effects of Ether, Brit. M. J. **2**: 148, 1945.

Beazell, J. M., and Ivy, A. C.: The Influence of Alcohol on the Digestive Tract, Quart. J. Alcohol **1**: 45, 1940.

Bogen, E.: The Human Toxicology of Alcohol. *In* Alcohol and Man, Emerson, H., editor, New York, 1932, The Macmillan Co.

Bruger, M.: The Effects of Alcohol on the Normal and Pathologic Kidney, Quart J. Alcohol **1**: 85, 1940.

Davenport, C. B.: The Effects of Alcohol on Animal Offspring, *In* Alcohol and Man, Emerson, H., editor, New York, 1932, The Macmillan Co.

Emerson, H. (Editor): Alcohol and Man, New York, 1932, The Macmillan Co.

Haggard, H. W., and Jellinck, E. M.: Alcohol Explored, New York, 1942, Doubleday Doran & Co.

McNally, W. D.: Toxicology, Industrial Medicine, Chicago, 1937.

Newman, H. W.: Acute Alcoholic Intoxication: A Critical Review, Stanford University Press, 1941.

Newman, H. W., and Lehman, A. J.: Nature of Acquired Tolerance to Alcohol, J. Pharmacol. & Exper. Therap. **62**: 301, 1938.

Newman, H. W., Lehman, A. J., and Cutting, W. C.: Effect of Dosage on Rate of Dissappearance of Alcohol From Blood Stream, J. Pharmacol. & Exper. Therap. **61**: 58, 1937.

Rotman, D. B.: Alcoholism a Social Disease, J. A. M. A. **127**: 564, 1945.

Webster, R. W.: Legal Medicine and Toxicology, Philadelphia, 1930, W. B. Saunders Co.

White, P. D., and Sharker, T.: Tobacco, Alcohol and Angina Pectoris, J. A. M. A. **102**: 655, 1934.

CHAPTER XII

DRUGS ACTING ON THE PERIPHERAL NERVOUS SYSTEM

I. PARASYMPATHETIC NERVOUS SYSTEM

THE AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system consists of that division of the nervous system which controls the functions of all tissues except those of the striated skeletal muscle. Thus, by the "autonomic nervous system" is meant the whole nervous mechanism that regulates the vegetative side of life—nutrition, reproduction, circulation, and body temperature. Broadly speaking, it controls all unstriated muscles, including heart and blood vessels, muscles of the bronchi, thoracic and abdominal viscera, external generative organs, erection of hairs, involuntary muscles of the eye, and the glands. In speaking of the functions of the autonomic system Claude Bernard said, "Nature thought it prudent to remove these important phenomena from the caprice of an ignorant will."

Winslow (1732), believing that this system controlled the sympathies of the body, introduced the term *sympathetic*. Bichat (1800) used the term *vegetative* to designate its control over essentially nutritive processes. Gaskell (1916) suggested *involuntary*, contrasting its activities with those of the voluntary system, governing muscular contractions. Langley (1921), finding the terminologies confusing, suggested the phrase autonomic nervous system, which includes all functions subject to involuntary nervous control such as the smooth and cardiac muscles and the glands. They are capable of functioning automatically when all connections with the cerebrospinal axis are severed. Their functions, however, are regulated and modified by central impulses.

Divisions of the Autonomic Nervous System.—The autonomic nervous system consists of two fairly distinct anatomical divisions which stand in more or less functional opposition to each other. The two divisions of the autonomic nervous system are: (1) the parasympathetic, craniosacral, or cholinergic division, and (2) the sympathetic (orthosympathetic), thoracolumbar, or adrenergic division.

Parasympathetic System.—The parasympathetic nervous system is characterized by its cranial fibers leaving the cord by way of the third, seventh, ninth, tenth, and eleventh cranial nerves. The sacral preganglionic fibers run in the visceral rami of the second, third, and fourth sacral nerves. The parasympathetic system is augmentor to the organs derived from endoderm. It supplies the eyes, upper part of the digestive tract, heart, lungs, salivary glands, blood vessels of the head, sweat glands, bladder and sexual organs, and the lower parts of the alimentary tract. (Fig. 5.)

Sympathetic Nervous System.—The sympathetic division is generally augmentor to organs derived from ectoderm. It consists of a chain ganglia lying outside of the central nervous system. These ganglia are connected with the spinal cord by means of white rami coming from the lateral gray horns and branches to the various visceral plexus. The ganglia, in turn, send gray rami to the peripheral nerves to supply vaso-

motor fibers to the blood vessels and secretory fibers to the skin. Fibers pass from the cerebral cortex to the hypothalamic region, thence to the pons and medulla and to the eighth cervical and first thoracic segments to the spinal cord, and emerge and pass in the cervical sympathetic chain to the superior cervical ganglia. The cervical sympathetic fibers supply the dilator pupillae, the orbital muscle of Müller, the involuntary levator muscles of the upper lid, the sweat glands, and the blood vessels of the face.

The innervation of the sweat glands is anatomically purely sympathetic, but it reacts pharmacologically as if it were parasympathetic. The *uterus* also occupies a peculiar position; its sympathetic innervations respond to both parasympathetic and sympathetic drugs. The innervation of *glands* derived from epidermis (sweat) receive their augmentor supply from sympathetic nerves; the parasympathetic augments the endodermal glands such as the pancreas, gastric mucosa, etc. The salivary glands probably have cells derived and innervated from both systems.

Chief Functions of the Autonomic System.—The details of the action produced by the autonomic nerves are complex but the chief functions are summarized in Table XII (Meyer, Gottlieb and Biedl).

Sympathetic and Parasympathetic Antagonism.—The sympathetic and parasympathetic nervous systems are essentially antagonistic. Pharmacologically, there is a certain amount of overlapping between the two systems. The sympathetic dilates the pupil, the parasympathetic contracts it; the sympathetic accelerates the heart, the parasympathetic slows it; the sympathetic contracts the arterioles, the parasympathetic inhibits vasoconstriction; the sympathetic inhibits peristalsis, the parasympathetic stimulates peristalsis; the sympathetic aids filling of the bladder by contracting the sphincter and inhibiting the detrusor muscle, the parasympathetic inhibits the vesical sphincter and stimulates the detrusor, thus causing emptying of the bladder. The sympathetic erects the hairs and causes sweating. The sympathetic is essentially catabolic, the adrenal glands and sympathetic together fitting the body for emergencies; the parasympathetic is anabolic, maintaining the metabolism, good health, and happiness of the individual.

Although the two divisions of the autonomic nervous system—parasympathetic and sympathetic—are anatomically quite distinct, a strict physiological antagonism does not exist. The state of activity of the organism, at the time of the nerve stimulation, determines in large part the response. The greater the level of activity, the less susceptible are the organs to stimulation, and the more reactive to depressants; the lower the level of activity, the more reactive to stimulation and the less responsive to inhibitory influences. For example, epinephrine has greater accelerating influence in complete heart block when the ventricular rate is slow than when it is fast.

Transmission of Nerve Impulses.—In 1904, T. R. Eliott suggested that sympathetic nerve impulses released a stimulating substance (epinephrine-like) at the nerve endings. In 1914, Dale, studying acetylcholine, noted that it produced effects similar to those caused by parasympathetic nerve stimulation. He noticed the brief duration of action and believed an esterase in the body rapidly hydrolyzed the acetylcholine to the less active choline. Otto Loewi contributed brilliant results of research in this field. His clinical experiments on frog hearts may well be mentioned: He noted that an accelerator (epinephrine-like) substance was liberated on stimulation of the

TABLE XII

EFFECT OF STIMULATION OF SYMPATHETICS AND PARASYMPATHETICS

ORGAN	SYMPATHETICS	PARASYMPATHETICS
Skin		
Pilomotor muscles	Contracted	--------
Sweat glands	Increased	Decreased
Eye		
Iris	Dilatation	Constriction
Ciliary muscle	Relaxed for far vision	Accommodation for near vision
Smooth muscle of orbit	Constriction	--------
Heart		
Rate	Accelerated	Slowed
Output	Increased	Decreased
Blood Vessels		
Coronary	Dilatated	Constricted
Skin and mucosa	Constricted	Dilatated
Muscle	Dilatated, constricted	Dilatated
Cerebral	Constricted	Dilatated
Pulmonary	Constricted	Dilatated
Abdominal viscera	Constricted	Dilatated
Lungs		
Bronchial glands	Inhibited(?)	Secretion
Bronchial muscle	Relaxed	Constricted
Stomach		
Motility and tone	Decreased	Increased
Secretion	Inhibited(?)	Increased
Sphincters	Contracted (usually)	Relaxed (usually)
Intestine		
Motility and tone	Decreased	Increased
Secretions	Inhibited(?)	Increased
Sphincters	Contracted (usually)	Relaxed (usually)
Gall Bladder and Ducts	Relaxed(?)	Contracted
Uterus		
Pregnant	Stimulated	Stimulated
Nonpregnant	Stimulated(?)	Stimulated or relaxed
Urinary Bladder		
Trigone and sphincter	Contracted	Relaxed
Detrusor	Relaxed	Contracted

TABLE XII—CONT'D

ORGAN	SYMPATHETICS	PARASYMPATHETICS
Ureter Motility and Tone	Decreased	Increased
Salivary Glands	Secretion (small amount, thick, mucinous)	Secretion (large amount, thin)
Lacrimal Glands	--------	Secretion
Nasopharyngeal Glands	--------	Secretion
Pancreatic Islets and Acini	--------	Secretion(?)
Liver	Glycogenolysis	--------
Adrenal (medulla)	--------	Secretion of epinephrine
Spleen (capsule)	Constricted	--------

sympathetic nerves in the frog's vagus. He noted that atropine and ergotoxine prevented slowing or acceleration of the rate of the heart, but did not prevent liberation of substances which slowed or accelerated a second heart which was connected in such a manner as to be bathed by the same fluid as nourished the first heart. Furthermore, he demonstrated that his "vagus substance" was an unstable choline-ester, capable of being hydrolyzed rapidly by an esterase in the heart muscle, and that physostigmine delayed this hydrolytic action. These phenomena, noted in the heart, have been duplicated in other organs of the body.

Cannon and his co-workers believe that the true sympathetic nerves, on stimulation, liberate two substances: "sympathin E," which stimulates distant motor sympathetic endings, and "sympathin I," which stimulates distant inhibitory endings. This concept has no analogy in the parasympathetic system, where acetylcholine acts on all cells sensitive to it, regardless of whether it was released by inhibitory or augmentory nerves.

The "vagus substance" of Loewi and acetylcholine are apparently identical. Both substances are dialyzable, are stable in acid media, are rapidly inactivated by blood or tissue esterase, and both are protected from inactivation by physostigmine.

Sympathin and epinephrine are also quite similar; they give similar colorimetric tests, produce similar sympathomimetic effects which are enhanced by cocaine, and both are easily destroyed by alkali. Sympathin, however, differs from epinephrine in its response after ergotoxine.

There are noteworthy exceptions to the statement that liberated acetylcholine initiates parasympathetic actions and that sympathins (E and I) initiate sympathetic effects. For example, sweat glands, though innervated by sympathetic fibers, form acetylcholine on stimulation. Likewise, some sympathetic nerves of certain blood vessels dilate through the action of acetylcholine mechanism. In order to name nerve fibers and impulses in functionally descriptive terms,

Dale suggested that the fibers which liberate acetylcholine be called *cholinergic*, and that the term *adrenergic* be given to those which liberate adrenalin-like substances.

The actions of atropine, pilocarpine, and acetylcholine on sweat glands and the apparent absence of any epinephrine effect may now be explained by the fact that the fibers are "cholinergic" although coming from the sympathetic system. Also, the vasodilator and nicotinic actions of acetylcholine are explained on the basis of the "cholinergic" nature of the preganglionic fibers and nerves to certain blood vessels.

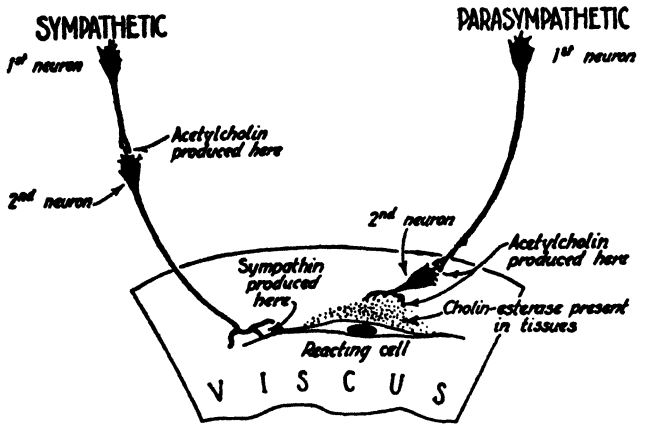


Fig. 6.—Balance between sympathetic and parasympathetic nerves and esterase (Myerson: Human Autonomic Pharmacology, J. A. M. A. 110: 101, 1938).

Summary.—Elliott, Loewi, Dale, Cannon, and their followers think that the theory of the two chemical mediators is an adequate explanation of nerve impulses. Many facts, however, are incompatible with this theory; for example, some of the actions of atropine on the bladder and also on the intestines are difficult to explain on the basis of this theory. We may summarize autonomic pharmacology as follows: Stimulation of the sympathetic fibers results in a secretion of an epinephrine-like substance, *sympathin* (Fig. 6), at the nerve endings, while stimulation of parasympathetic fibers yields *acetylcholine* at the nerve endings (Fig. 7). Each of these substances stimulates the visceral organ to produce respective sympathetic and parasympathetic effects. The parenteral injection of adrenalin results in sympathetic effects while that of acetylcholine produces parasympathetic effects. Each of these autonomic humoral substances are destroyed by enzymes. *Aminoxidase* destroys adrenalin but much more slowly than does *choline esterase* hydrolyze acetylcholine (Figs. 6 and 7). The action of acetylcholine at these end plates is nicotinic in nature, being abolished by curare. Recently, considerable attention has been paid to the possible role of acetylcholine in synaptic transmission in the central nervous system.

Clinical Importance of Autonomic Nervous System.—The autonomic nervous system reaches to every part of the human body and consequently a knowledge of this complex system and of the effects of drugs on it is of primary importance in medicine. Since all activities which are essential to man as an individual occur at the vegetative

level, it is strange that the autonomic nervous system, up until just recently, has received so little attention from the medical profession. When we realize that there is possibly no function of the autonomic system that cannot be directly or indirectly modified by the action of drugs, and that there are thousands of drugs, any one of which can act on some part of this complex mechanism, then only can we appreciate its true importance.

There are many diseases that are due to the failure of the autonomic system to function properly. Dysfunction of the autonomic system, no doubt, is an important factor in such diseases as bronchial asthma, angioneurotic edema, urticaria, migraine, angina pectoris, diabetes insipidus, auricular flutter, and many more. Hence, a thorough knowledge and understanding of the whole autonomic nervous mechanism is a necessity for the present-day practice of medicine. We should bear in mind that the administration of drugs should be based on a thorough knowledge of their effects on normal and abnormal physiological processes. The clinician should make his diagnosis in terms of disorganized processes and then administer that drug which will best aid the organism to return to normal.

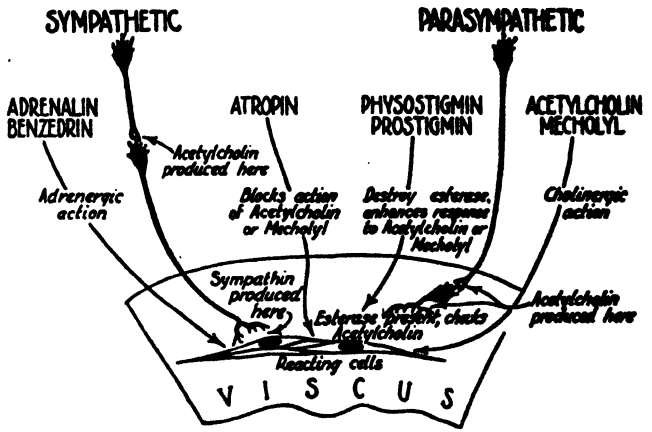


Fig. 7.—Working hypothesis of human autonomic pharmacology (Myerson: Human Autonomic Pharmacology, J. A. M. A. 110: 101, 1938).

AUTONOMIC DRUGS

The term "autonomic drugs" is generally applied to those drugs which act chiefly on the autonomic nervous system to mimic or oppose the peripheral effect of nerve impulses of the autonomic nervous system. They may be grouped into four main classes of drugs: (1) the parasympathomimetic, which tend to produce stimulating effects on the parasympathetic nervous system; (2) parasympatholytic (or anti-parasympathomimetic), which tend to paralyze the parasympathetic nervous system; (3) the sympathomimetic drugs, which tend to stimulate, and (4) the sympatholytic (or anti-sympathomimetic) which tend to paralyze or inhibit the sympathetic (or orthosympathetic) nervous system.

Certain discrepancies are found in the effects produced by the various groups of autonomic drugs. The uncertainty that prevails regarding

TABLE XIII

AUTONOMIC DRUGS

Parasympathomimetic (stimulation)	Parasympatholytic (inhibition)
Acetylcholine	Atropine
Pilocarpine	Scopolamine
Physostigmine (Eserine)	Hyoscyamine
Neostigmine (Prostigmine)	Stramonium
Methacholine (Acetyl-beta-methylcholine)	Homatropine
Carbachol (Carbamylcholine chloride)	Eucatropine
Di-isopropyl Fluorophosphate	Homatropine methylbromide
Choline	Eumydrine
Arecoline	
Muscarine	
Sympathomimetic (orthosympathomimetic) (stimulation)	Sympatholytic (orthosympatholytic) (inhibition)
Epinephrine	Ergotoxine
Ephedrine	Ergotamine
	Yohimbine
Synthetic Sympathomimetic Drugs	Synthetic Sympatholytic Drugs
Amphetamine (Benzedrine)	Dioxane Derivatives
Phenylephrine (Neosynephrine)	Dibenzamine Hydrochloride
Kephrine	Imidazoline Derivatives
Paredrine	
Propadrine	
Naphazoline (Privine Hydrochloride)	
Tuamine	
Vonedrine	
Tyramine	

the exact mode and site of action of these drugs makes it difficult to adopt a classification that does not contain certain disagreements. It should be realized that since there is a close interrelationship of the two branches of the autonomic system supplying the various organs, stimulation of one branch may tend to a compensatory stimulation of the other; thus, many unpredictable effects or seemingly discrepancies arise. Furthermore, parasympathomimetic drugs may, especially in large doses, have nicotinic action which produces sympathomimetic as well as parasympathomimetic effects. It should also be kept in mind that autonomic drugs frequently have a central effect which may at times be more apparent than their peripheral effects.

This simple classification requires considerable qualification, for the real actions of these drugs are more complex than are indicated by the simple arrangement given. In general, we may say that acetylcholine produces all the effects produced by stimulation of the parasympathetic system and that these effects are paralyzed by atropine. Acetylcholine, however, produces many other actions which are not produced by stimulation of the parasympathetic.

In general, we may say that epinephrine and pilocarpine produce almost exactly the same effects as are produced by stimulating the sympathetic and parasympathetic nerves respectively. The action of epineph-

rine, however, includes additional actions not identified with sympathetic stimulation, i.e., increase in metabolism, etc.

Ergotoxine and ergotamine antagonize adrenalin and sympathetic stimulation, but they also possess stimulant effects on smooth muscle. Pilocarpine apparently acts by stimulation of the "receptive mechanism" of the parasympathetic nerve ends, while physostigmine evidently acts by preventing the destruction of acetylcholine (which stimulates the parasympathetic) by choline-esterase. In addition, pilocarpine continues to act after denervation of the pupil, but physostigmine no longer acts after denervation.

These examples indicate the general complexity of all drug action. There are, however, certain general actions with which we should become familiar, even though other exceptional and complex actions of less importance are produced.

PARASYMPATHOMIMETIC DRUGS

The parasympathomimetic drugs or the drugs which produce the action of acetylcholine, in general may be said to increase the activity of the parasympathetic nervous system. Members of this group include acetylcholine, pilocarpine, physostigmine, neostigmine, methacholine, carbachol, di-isopropyl fluorophosphate, choline, arecoline, and muscarine.

Acetylcholine

Acetylcholine is a derivative of choline. The acetylation increases the depressor effect 100,000 times, and the toxicity only three times. Recent investigation has developed strong evidence to show that the chemical mediator of parasympathetic nerve impulse is acetylcholine. It is very similar to Loewi's "vagus substance." Acetylcholine apparently is concerned with the synaptic transmission of nerve impulses in certain autonomic ganglia. Extracts of the vagus nerve give tests for acetylcholine, the only choline ester which has been isolated from animal tissues. The drug is extremely potent in high dilutions. The physostigminized dorsal muscle of the leech will contract when placed in a 1:20,000,000,000 dilution of acetylcholine.

The action of acetylcholine is similar to the action produced by stimulation of the parasympathetic nervous system. The effect, which occurs in dilutions as high as 1:100,000, is abolished by atropine. Use is made of this action to assay atropine. Acetylcholine is antagonized by atropine. Our present knowledge seems to indicate that the antagonism includes also that of "cholinergic" nerve endings whenever they occur, for example, in postganglionic sympathetic nerves to sweat glands and certain blood vessels, preganglionic fibers to autonomic ganglia and somatic nerves to voluntary muscle.

Acetylcholine chloride has been used for treatment of spasm of the involuntary muscle, as in lead colic. The dose is 1 to 3 grains (0.06 to 0.18 Gm.) once or twice a day subcutaneously. The well-established parasympathetic stimulatory action of acetylcholine is of little therapeutic value because of the instability of the drug and its fleeting action.

Pilocarpine

Pilocarpine is the principal alkaloid obtained from the leaves of a South American shrub, *Pilocarpus jaborandi*. The plant usually assays about 0.6 per cent alkaloid. The drug, which is also prepared synthetically, readily forms crystalline soluble salts with acids.

Other drugs obtained from *Pilocarpus jaborandi* are iso-pilocarpine and pilocarpidine. They have similar actions but are markedly unequal in power, iso-pilocarpine being the strongest and pilocarpidine the weakest.

Pharmacological Action.—Pilocarpine is of importance chiefly because of its diaphoretic, diuretic, sialogogue, and miotic action. It acts most powerfully on the pupil of the eye, on the secretion of sweat, and on the movements of the gastrointestinal tract. The chief action of pilocarpine is the stimulation of the "receptive substances" directly, by acting peripheral to the nerve endings and causing parasympathetic effects, e.g., cardiac inhibition, contraction of smooth muscle of the eye, bronchioles and alimentary tract, and secretion from the salivary, bronchial, and gastric glands. (See Table XIV). It also *stimulates the sweat glands* which receive excitatory fibers from the sympathetic. The mechanism does not degenerate after section and degeneration of the nerve, hence, pilocarpine acts after the nerves are destroyed.

Absorption and Excretion.—Pilocarpine is readily absorbed from the skin, mucous membrane, and from other tissues. It is rapidly excreted in the urine, saliva, and sweat. There is no cumulative action.

Action on the Eye.—Pilocarpine solutions instilled in the eye cause (1) contraction of the pupil, reaching its height in one-half hour and subsiding after three hours; (2) stimulation of ciliary muscle, resulting in spasm of accommodation and adjustment of the eye for near vision, and (3) a preliminary rise in intraocular tension, which may last for one-half hour and be followed by a fall in pressure. The fall in intraocular tension follows contraction of the pupil and results from an increased escape of fluid into the spaces of Fontana, which are opened by contraction of the ciliary muscle. The contraction of the pupil is due to stimulation of the endings of the oculomotor nerve in the constrictor muscle.

Action on Glands.—Pilocarpine increases secretion of saliva, sweat, tears, mucus, gastric juice, pancreatic juice, and, no doubt, milk and intestinal juice. The amount of sugar in milk is increased by pilocarpine. Gastric acidity is probably not increased by pilocarpine. There is no increase in urine and bile, and these secretions are not influenced by nerves. This indicates that the action is not directly on gland cells. Atropine will stop increased secretion, which indicates that the action is not on the secretory cells, since atropine does not act on gland cells. Section of the secretory nerves does not alter the action of pilocarpine.

Pilocarpine is the most potent *diaphoretic* at our command; five to nine pounds of body weight may be lost through the skin after a single dose of pilocarpine. The secretion of sweat is due to glandular activity, and follows excitation of secretory nerves. The sweat glands are under control of the sympathetic system, although the action of drugs would indicate that the sweat glands belong to the parasympathetic. The diaphoretic value of this drug is chiefly in conditions in which there is an excess of fluid in the tissues, and in which kidneys are not excreting properly, as in nephritis with uremia, and in dropsy. Its use is also indicated in pleural and pericardial effusions.

Action on Unstriated Muscle.—Pilocarpine causes stimulation of the receptive substance of the parasympathetic nerves, causing contraction of most unstriated muscles. The intestines are especially stimulated (Fig. 8), causing diarrhea and colic. The bronchi, bladder, and pupils are contracted. The uterus and smooth muscle of the blood vessels do not appear to be affected.

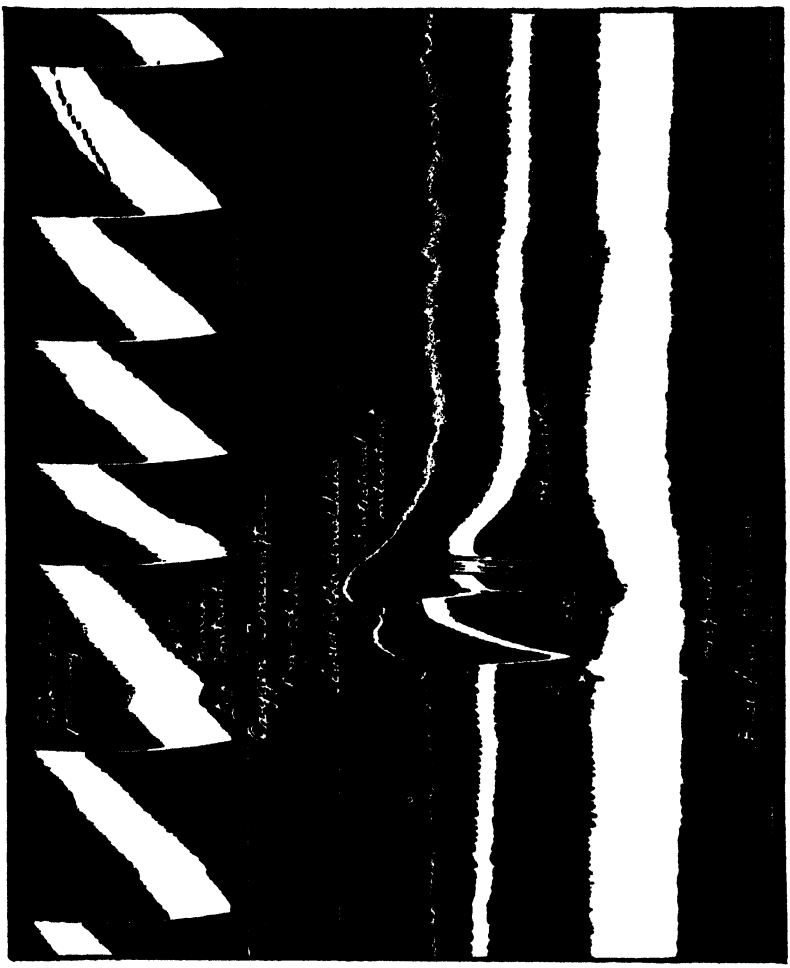


Fig. 8.—Tracing showing the action of pilocarpine on the rate of oxygen consumption, intestinal contractions, blood pressure, and respiration. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

Action on Circulation.—Pilocarpine slows the heart in large doses through stimulation of the cardio-inhibitory vagus nerve terminals (Fig. 8). A moderate fall of blood pressure (Fig. 8) may occur in consequence. In some instances the drug may accelerate the heart slightly through depression of the vagus centers, causing a rise in blood pressure. Toxic doses depress the cardiac muscle directly and depress the vasoconstrictor center, causing vessel dilatation; a fall of blood pressure results.

Action on Respiration.—Excessive doses depress respiration and cause increased bronchial secretion, and contraction of the bronchi, thus tending to promote difficulty in breathing. (Fig. 8.)

Action on Central Nervous System.—Pilocarpine has little effect on the nerve centers of the brain. The mind remains clear even with toxic doses. The spinal cord and medulla are depressed by large doses.

Toxicology.—Poisoning by pilocarpine is usually accidental. The symptoms of acute poisoning are increased salivation, lacrimation, perspiration, and flushing of the skin. Later, thirst, abdominal cramps, vomiting, pain in eyeballs, myopia, dimness of vision, giddiness, and convulsions may occur, and finally cardiac weakness and cyanosis. Death follows respiratory failure. Signs of renal irritation may be present.

The lesions at *autopsy* are mainly those of asphyxia, cyanosis, and edema of the lungs. Death may occur at various lengths of time after poisoning. Serious and even *fatal results* have followed the injection of 0.02 gram (⅓ grain).

TREAT poisoning by stomach lavage and by the immediate hypodermic injection of atropine in full doses of 0.0012 to 0.004 gram (1/50 to 1/15 grain), as a physiological antidote. With appearance of symptoms of spinal or circulatory depression, stimulants, such as strychnine, caffeine or hot strong coffee, and ammonia preparations, are indicated, together with artificial respiration.

Pilocarpine and Atropine Antagonism.—The action of pilocarpine (also muscarine and physostigmine) on the myoneural junctions is completely neutralized by atropine. This antagonism does not extend to the brain, which is often the point of danger in poisoning. Consequently, pilocarpine is not an effective antidote in atropine poisoning. Although the peripheral antagonism is not fully understood, a small amount of atropine will neutralize the action of pilocarpine; the neutralization of the atropine action is more difficult and the action is not quantitatively mutual.

SUMMARY OF THE EFFECTS OF DRUGS UPON THE PUPIL AND CILIARY MUSCLE.—Drugs which cause pupillary dilation are called *mydriatics;* those which cause constriction, *miotics*. Drugs which paralyze the ciliary muscles are called *cycloplegics*.

Mydriasis is caused by drugs which:

1. Paralyze the peripheral constrictor (parasympathetic) mechanism, i.e., atropine, homatropine. Atropine is also cycloplegic, homatropine much less so.
2. Stimulate the dilator (sympathetic) mechanism, i.e., epinephrine, cocaine. These drugs do not affect accommodation.

Miosis is caused by drugs which:

1. Stimulate the peripheral constrictor mechanism, i.e., pilocarpine, physostigmine, muscarine. These drugs also cause spasm of the ciliary muscles.
2. Diminish the inhibition of the constrictor center, for example morphine.
3. Drugs which stimulate the constrictor center, as picrotoxin.

TABLE XIV

SUMMARY OF PILOCARPINE ACTION

(Typical Parasympathetic Stimulant)

ACTION	USE	TOXIC SYMPTOMS
I. Eye Stimulation of Oculomotor Nerve. A. Miosis. B. Lessens intraocular pressure. C. Accommodation fixed for near vision. D. Improves circulation.	 A. Miotic. B. Used in glaucoma. D. Absorption of opacities and acute keratitis.	 Contracted pupil.
II. Glands. Increases gland secretions.	Relieves congestion of midear, eye, and labyrinth affection.	Salivation. Profuse nasal, throat and lacrimal secretions.
III. Circulation. Improves skin circulation.	Hair tonics, pruritus, eczema.	Skin flushed.
IV. Heart. (Chiefly depression.)	No therapeutic uses.	Slow feeble pulse. Low blood pressure.
V. Alimentary Tract. Increases peristalsis of stomach and intestines and increase of sphincter's tone.	Stimulates peristalsis.	Abdominal cramps, diarrhea, nausea, vomiting.
VI. Bronchi. Increased bronchial secretions and constriction.	Expectorant.	Labored breathing.
VII. Bladder. Increased bladder tonus. Repeated micturition.	No therapeutic use.	Repeated micturition. Tenesmus.
VIII. Sweat Glands. Increased action of sweat glands.	Diaphoretic.	Profuse sweating. Weakness.

Therapeutic Uses.—Pilocarpine is seldom prescribed. It is best administered by the physician himself by subcutaneous injection of pilocarpine salts. Its preparations, if administered orally, are uncertain in action and may cause nausea and vomiting.

Ophthalmic Disorders.—Pilocarpine is used to aid adsorption of vitreous opacities. De Schweinitz recommends the hypodermic administration of pilocarpine, 0.006 to 0.03 gram (1/10 to 1/2 grain), daily, for opacities of the vitreous humor. As a miotic, one or two drops of a 0.5 to 2 per cent solution every hour until the pupil is sufficiently contracted, is recommended. Pilocarpine hydrochloride, 1:200, is used in glaucoma to lessen intraocular tension; however, eserine is usually preferred. As a tonic to the eyes following excessive use, instill in the eye a few drops of pilocarpine solution (0.006 Gm. pilocarpine, 0.25 Gm. of boric acid, 30 cc. distilled water).

Diaphoretic.—Pilocarpine (0.006 Gm.) may be administered hypodermically for its diaphoretic effect, especially in nephritis. About 6 to 8 grams of nonprotein nitrogen may be eliminated in this manner along with several liters of fluid. The side reactions, such as salivation, diarrhea, weakness, etc., have made such therapy very unpopular.

Pilocarpine nitrate, 0.005 gram (1/12 grain) hypodermically, may be given for excessive dryness of the mouth in such conditions as botulism poisoning, etc. However, the sweating and depression resulting from its use may outweigh its benefit.

Respiratory Diseases.—In early acute bronchitis, 2 to 3 mg. (1/20 to 1/10 grain) of pilocarpine nitrate may be administered orally, three times daily to increase bronchial secretions. In chronic bronchitis the same treatment may aid elimination of thick and tenacious secretions.

Skin Disorders.—In doses of just sufficient amounts to produce free diaphoresis, it is indicated as an antipruritic in generalized acute eczema, urticaria, pruritus, and scleroderma. In alopecia the use of pilocarpine locally or hypodermically apparently encourages some temporary growth of hair.

Functional Test of Autonomic System.—Pilocarpine may be used to test the sweating response of the autonomic nervous system. Sweating, which results if the autonomic system is intact, is detected by the red color imparted to an alcoholic solution of cobalt blue previously painted on the skin. This may be of importance in testing for complete sympathetic fiber denervation, and assist in the diagnosis of such diseases as postural hypotension.

Miscellaneous Uses.—Pilocarpine may prove efficient in the treatment of aural vertigo. Cases of Ménière's disease have responded to this drug. In deafness and vertigo due to inflammation of the labyrinth injection of 0.01 to 0.02 gram (1/6 to 1/3 grain) of pilocarpine may prove of value. Pilocarpine is of some value in atropine poisoning but is less efficient than atropine for pilocarpine poisoning.

PREPARATIONS

Pilocarpine Nitrate, *Pilocarpinae Nitras*, U.S.P., B.P. *Dosage:* 0.005 Gm. (1/12 grain).

Pilocarpine Hydrochloride, *Pilocarpinae Hydrochloridum*, N.F. *Dosage:* 0.005 Gm. (1/12 grain).

Physostigmine

Physostigmine (eserine) is the chief alkaloid obtained from Calabar beans or "ordeal beans," seeds of a West African plant called *Physostigma venenosum*. The name, "ordeal bean," comes from use of the seed by the tribes of West Africa in their trials by ordeal.

If, after eating the beans, the defendant showed signs of poisoning, such as salivation, vomiting, giddiness, etc., he was judged guilty. The plant contains 0.15 per cent of alkaloids, the most important of which include physostigmine, eserídine, eseramine, and calabrine. Physostigmine ($C_{15}H_{21}O_2N_3$) is a crystalline alkaloid sparingly soluble in water but soluble in alcohol. It is chiefly used as the salicylate. Solutions of physostigmine deteriorate in light and at high temperatures, and show a reddish coloration.

Pharmacological Action.—The miotic and peristaltic actions of physostigmine are of great importance in medicine.

Absorption and Excretion.—Physostigmine is readily absorbed and excreted, partially by the urine, but most of it is destroyed in the tissues. A small amount is excreted in the bile and saliva.

Mode of Action.—Physostigmine acts by inhibiting the esterase (choline-esterase) which destroys the acetylcholine normally produced at the nerve endings. Its action is sensitization rather than direct stimulation of nerve endings, as with pilocarpine. Physostigmine acts only if the nerve is intact, but pilocarpine is effective if the nerve is either cut or anesthetized.

The pharmacological action of physostigmine resembles that of pilocarpine in many respects but produces more powerful contractions of smooth muscle of the eye and intestine. The glandular stimulation is less marked than with pilocarpine. On the central nervous system the effects are mainly paralyzing.

Action on the Eye.—In the eye, physostigmine causes contraction of the pupil (miosis) by stimulation of the motor oculi nerves peripherally. It also diminishes intraocular tension. The extreme contraction of the pupil uncovers the spaces of Fontana and permits drainage of excess fluid, thus lowering intraocular tension.

Fig. 9 shows diagrammatically the sites of action of various miotic and mydriatic drugs.

Action on Gut.—Physostigmine increases peristalsis. It acts as a powerful stimulant to unstriated muscle of the stomach and bowels, and increases their secretions. The action on the peristaltic movements may be so violent as finally to cause tetanus and contractures. This action is not influenced by the higher nerve centers, but is produced entirely by peripheral motor excitation.

For constipation (Tice's *Practice of Medicine*):

℞

Podophyllum	0.30 Gm. (gr.v)
Physostigmine Extract	0.50 Gm. (gr.viij)
Glycyrrhiza Extract	q.s.

M. fac pilulas No. xxx.

Sig.: One pill twice daily.

Action on Circulation.—Toxic doses cause a rise in blood pressure, due in part to direct stimulation of the cardiac muscle and its ganglia. Some of the action, however, may be due to the powerful intestinal movements caused by the expelling of blood from the mesenteric region, or to the narrowing of the lumens of the arterioles. There is also a slowing of the pulse. The action on the vasomotor centers is in doubt.

Action on Central Nervous System.—The main action of the drug is to depress the motor centers of the spinal cord. The respiratory center of the medulla is depressed, but the cerebral cortex and the sensory nerves suffer no loss of function, and the motor nerve-trunks are little affected by ordinary doses.

Physostigmine also excites voluntary motor endings, hence, to some degree, is an antidote to magnesium poisoning and alleviates symptoms of myasthenia gravis.

Toxicology.—Toxic doses of physostigmine produce extreme muscular debility, abdominal pain, dyspnea, and giddiness, followed by paralysis of voluntary muscles, muscle twitching, and miosis. When taken orally physostigmine causes paralysis of the pharyngeal muscles by direct muscular action or action on the nerve-endings. Respiration is depressed and usually the blood pressure falls; the action on the blood pressure, however, is variable. Death may occur from respiratory failure or cardiac damage.

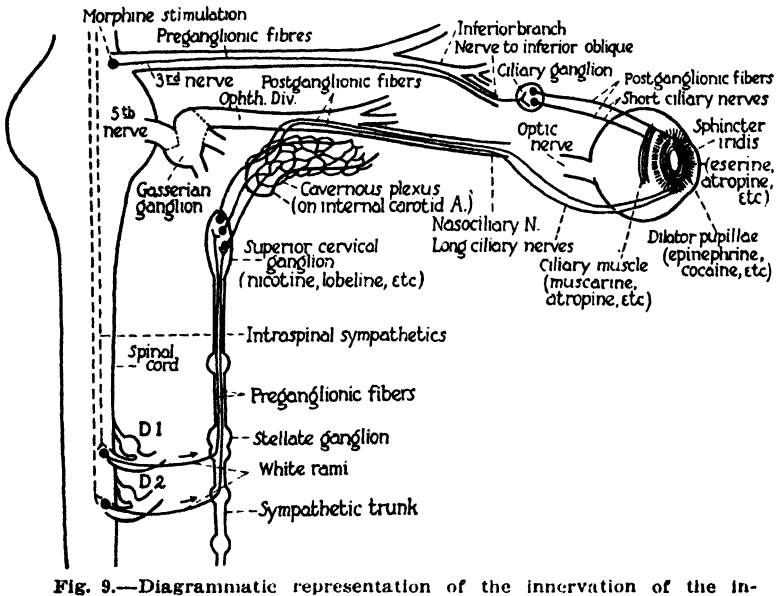


Fig. 9.—Diagrammatic representation of the innervation of the intrinsic muscles of the eye with the sites of action of mydriatic and miotic drugs. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

TREATMENT.—If the crude drug has been swallowed, lavage of the stomach or an emetic is indicated. Large doses of tea or tannin (2 Gm. in 120 cc. water) may be given orally after emptying the stomach. As a physiological antidote, administer hypodermically 0.1 cc. of a 1 per cent solution of atropine as required. Strychnine nitrate, 0.005 gram (1/12 grain), may be administered hypodermically. Stimulants, such as strong coffee or aromatic ammonia spirit (2 to 4 cc.), may be required.

Therapeutic Uses.—The salicylate is chiefly employed hypodermically by the physician, but is rarely prescribed.

Eye Diseases.—In the treatment of *glaucoma* 0.1 to 0.2 per cent solutions are instilled in the eye two to five times daily. This treatment reduces the intraocular tension and pain. The effects may be temporary or prolonged; treatment may bring about cure. *Synechia:* In cases

of attachment of the iris to the lens, physostigmine may be used alternately with atropine. The alternate contraction and dilatation are effected to break up adhesions; 0.25 to 1.0 per cent solutions are used. *As miotic:* Instillations of physostigmine salicylate (drop doses of 0.25 per cent solution hourly for three hours) may be used to overcome atropine mydriasis. The drug is irritating and may cause conjunctivitis, hence oily solutions of the free alkaloid may be used. The instillation may have to be repeated to overcome the persistent effect of atropine.

Intestinal Diseases.—In the treatment or prevention of *postoperative intestinal atony* physostigmine, hypodermically in doses of from 0.5 to 1 mg. (1/120 to 1/60 grain), is indicated. The dose may be repeated after several hours. *Intestinal and bladder atony* respond well to physostigmine administration. In paralytic ileus and other forms of intestinal distention, administer orally, 0.001 to 0.002 gram (1/60 to 1/30 grain).

Rheumatic Affections.—Physostigmine has been recommended (Cohen et al., 1946) for the treatment of rheumatoid arthritis. *Procedure:* Give 1/100 grain (0.6 mg.) each of physostigmine salicylate and atropine sulfate simultaneously. If no relaxation of muscle is obtained, the physostigmine is increased to 1/30 grain (1.2 mg.), the dose of atropine being increased or decreased depending on the reaction encountered. Reduce physostigmine or increase atropine if patient complains of dizziness, salivation, nausea, or pain in the abdomen.

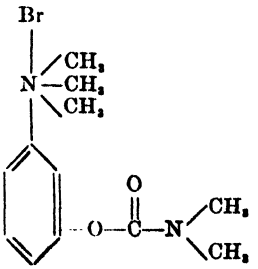
In *paroxysmal tachycardia, thyrotoxic tachycardia,* etc., administer orally, 0.001 to 0.002 gram (1/60 to 1/30 grain). Caution: Some danger of heart block and provocation of asthmatic attacks.

PREPARATION

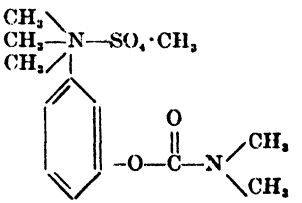
Physostigmine Salicylate, *Physostigminae Salicylas,* U.S.P. (Eserine Salicylate). *Dosage:* Internally, 0.002 Gm. (1/30 grain). Externally (should be freshly prepared) from 0.1 to 1 per cent.

Neostigmine (Prostigmine)

Neostigmine (Prostigmine) is a new synthetic compound resembling physostigmine, but differs from this alkaloid, chemically, by its less complicated structure and its greater stability. It is available only in the form of its salts, chief of which are neostigmine bromide and neostigmine methylsulfate.



Neostigmine Bromide



Neostigmine Methylsulfate

Neostigmine is a white crystalline substance, soluble in water and alcohol.

Pharmacological Action.—Neostigmine is less active on the eye than physostigmine, producing less miosis and less spasm of accommodation. It has less vagus-stimulating effect and therefore is less depressant to the heart. It is active on the intestine, increasing peristalsis and tonus. The action on skeletal muscle is similar to that of physostigmine. Its mode of action is apparently the same as for pilocarpine.

Neostigmine is readily absorbed following subcutaneous and intramuscular injection. Larger doses are required for oral administration. Whereas from 0.5 to 2 mg. are indicated for parenteral use, 30 mg. may be necessary for oral use. Toxic symptoms and treatment are the same as for physostigmine.

Therapeutic Uses.—*Intestinal and Bladder Atony.*—Neostigmine is indicated in intestinal and bladder atony in doses ranging from 0.5 to 1.0 mg. given hypodermically. The use of neostigmine for the prevention and treatment of intestinal and bladder atony is based on its action as a *vagotonic agent.*

Myasthenia Gravis.—Striking results have followed the use of neostigmine in cases of myasthenia gravis. The improvement starts in ten to thirty minutes and lasts for about six hours. A completely helpless patient may be made practically normal by this treatment. There may follow a certain degree of depression and increased muscular weakness. Its *anticurare-like* action is the basis of application in the treatment of this disease. It is possible that some of the action is due to the inhibition of the cholinesterase. *Dosage:* Neostigmine bromide capsules or tablets 15-30 mg. or ¼ to ½ grain, 3 times daily. *Neostigmine Methylsulfate* solution in sterile water, 0.05 per cent; 1 cc. containing ½ mg. or $\frac{1}{120}$ grain neostigmine methylsulfate subcutaneously or intramuscularly diagnostically in myasthenia gravis and during the acute crises of the disease.

Postoperative Distention and Ileus.—Harger and Wilkey (1938), Cook County Hospital, used neostigmine methylsulfate (1:4,000 solution) subcutaneously in doses of 1, 2, or 3 cc. every two hours until distention was relieved.

Neostigmine may be used in the treatment of severe *periodic headaches* by administering desensitizing doses. *Procedure:* 15 mg. tablet of neostigmine dissolved in 1 oz. of water and administered as follows: On first day, 1, 2, and 3 drops were given morning, noon, and night, respectively. The increase of 1 drop per dose was maintained until 30 drops were given each day for 1 week and then 3 times per week, for an indefinite period.

Poliomyelitis.—Neostigmine was found to assist in causing relaxation in spastic muscles (Fox and Spankus, 1945). Neostigmine methylsulfate is used subcutaneously or the bromide salt is given orally. *Dosage:* For *adults* $\frac{1}{40}$ to $\frac{1}{30}$ grain (1.5 to 2 mg.) of neostigmine methylsulfate together with $\frac{1}{100}$ grain (0.6 mg.) of atropine sulfate. For *children* (12 to 14 years) give ½ grain (30 mg.) neostigmine bromide and $\frac{1}{200}$ grain (0.3 mg.) of atropine sulfate three times a day.

Rheumatic Affections.—Neostigmine has been used to relieve painful spasms of muscles. Physostigmine may be more effective. (Cohen et al., 1946.)

Sinus Tachycardia.—Neostigmine methylsulfate (1 mg.) by injection (vagus stimulation) has been reported useful in aborting attacks of sinus tachycardia (Waldman, 1944). Neostigmine bromide tablets

(15 mg.) four times daily are reported as effective in preventing recurrences.

Spider Bite.—The intramuscular injection of 2 cc. of 1:2,000 neostigmine methylsulfate and 1/150 grain (0.4 mg.) of atropine has been reported as giving immediate relief. (Bell and Boone, 1945.)

Diagnostic Purposes.—Neostigmine may be used to differentiate myasthenia gravis from other neuromuscular disorders, since in this disease a remarkable tolerance to the drug is developed.

Undesirable parasympathiomimetic effects, such as salivation, perspiration, bradycardia, and gastrointestinal upset are counteracted by the concomitant administration of atropine.

Recently, neostigmine has been used in the treatment of *delayed menstruation.* Its use is based on the belief that inhibition of the destruction of acetylcholine, effected by neostigmine, leads to vasodilation and hyperemia of the uterus, which is thought to be one of the determining factors in the onset of menstrual bleeding.

Preparations

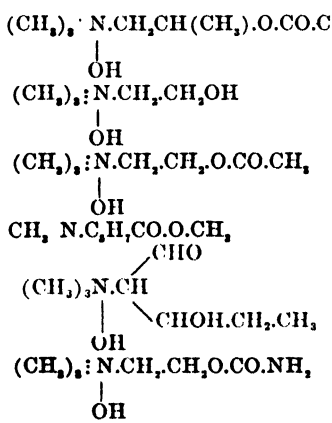
Neostigmine Bromide, *Neostigminae Bromidum,* U.S.P. *Dosage:* 15 mg. (1/4 grain).

Neostigmine Bromide Tablets, *Tabellae Neostigminae Bromidi,* U.S.P. *Dosage:* Usual size contains 15 mg.

Neostigmine Methylsulfate, *Neostigminae Methylsulfas,* U.S.P. *Dosage:* Subcutaneous, 0.5 mg. (1/120 grain).

Neostigmine Methylsulfate Injection, *Injectio Neostigminae Methylsulfatis,* U.S.P. *Dosage:* Usual ampul sizes contain 0.25 mg. and 0.5 mg. in 1 cc.

Choline and Its Esters



Methacholine

Methacholine is a choline derivative occurring as a white, crystalline hygroscopic powder, soluble in water and in alcohol, insoluble in benzene and ether. While it has similar pharmacological effects, there are striking differences which enhance its value as a therapeutic agent.

Pharmacological Action.—This drug stimulates the receptive mechanisms of organs innervated by the parasympathetic nervous system and other cholinergic nerves. A marked antagonism exists between metacholine and atropine. The drug differs from acetylcholine in

being almost free from nicotine-like effect, in being partially active orally, and in being more stable and thus producing a longer action following administration. The "muscarine" effect of this drug is marked.

The three main actions of methacholine are: (1) its powerful stimulation of the parasympathetic system, i.e., an inhibition of the heart with slowing; (2) its dilating action on arterioles (since arterioles have no parasympathetic innervation, the explanation is that certain sympathetic fibers to the blood vessels are "cholinergic" and cause vasodilatation when stimulated); (3) its stimulating action upon smooth muscle of the bronchi, stomach, intestine, bladder, and uterus.

Toxicology.—Since the range of dosage is very wide, toxic manifestations should be watched for, the most serious of which is cardiac arrest. Starr (1936) reports a systole lasting for seventy seconds. In normal persons, 10 to 20 mg. subcutaneously cause an immediate flushing of the face and neck, sweating, salivation, lacrimation, and a slight fall of blood pressure. There may be a transient increase in pulse rate. The symptoms pass off in ten to fifteen minutes. Oral doses may cause gastric irritation but rarely other symptoms, such as flushing, sweating, etc. Less toxic reactions such as precipitation of asthmatic attacks in asthma patients, dyspnea, epigastric discomfort, vomiting, and disturbances in accommodation are common. These symptoms may be relieved by injection of atropine.

Idiosyncrasy to methacholine may result in difficulty in breathing. If this is observed, stop drug, place patient in sitting position, and administer $\frac{1}{120}$ grain of atropine sulfate subcutaneously.

Therapeutic Uses.—*Paroxysmal Auricular Tachycardia.*—Methacholine is injected subcutaneously in doses of 20 to 40 mg. or $\frac{1}{3}$ to $\frac{2}{3}$ grain dissolved in sterile water. The patient is put to bed. If the arrhythmia persists, massage the site of injection and exert alternate pressure over the carotid sinuses. A second injection may be indicated after thirty minutes. This drug, which is effective in over 80 per cent of the cases, acts by vagal stimulation, hence larger doses (50 to 80 mg.) are indicated for elderly patients whose vagal tone is very low. In asthmatic patients it should not be employed under any circumstance. Atropine, $\frac{1}{50}$ grain hypodermically, is the antidote.

Peripheral Vascular Disease.—The beneficial action of methacholine upon peripheral vascular diseases is dependent upon their ability to relax vascular spasm, to produce a regional diaphoresis, and to relieve anoxemia, thus increasing the local circulation and consequently promoting the removal of waste products. It is the drug of choice in peripheral vascular diseases.

In overcoming vascular spasm due to moderate exposure to cold oral doses of from 0.05 to 0.1 Gm. ($\frac{3}{4}$ to $1\frac{1}{2}$ grains) of methacholine are effective. In *Raynaud's Disease, scleroderma,* and *ulcers* the effective oral dose may be somewhat higher. In general the therapeutic effective oral dose for methacholine ranges from 0.2 to 0.5 Gm. (3 to $7\frac{1}{2}$ grains) two or three times daily. Administer by dissolving in a little water and then adding to milk to disguise the taste. The subcutaneous dose for Raynaud's disease, scleroderma, and ulcers should be limited to 0.01 Gm. ($\frac{1}{6}$ grain) for initial injection; if well tolerated the dose may be increased to 0.025 Gm. ($\frac{3}{8}$ grain).

Chronic Rheumatoid Arthritis.—For application of methacholine by iontophoresis it is customary to use a 1:500 to 1:200 solution of the drug in distilled water. The solution is applied by moistening the positive electrode fabric which is placed over or near the part to be treated. The strength and duration of the current regulate the

dosage and should be applied gradually and within the tolerance of the patient. The initial treatment should not exceed 5 to 10 milliamperes in thirty minutes. Subsequent treatments usually require from 25 to 30 milliamperes for twenty to thirty minutes. Three or four days are allowed between treatments. In chronic rheumatoid arthritis the treatments may be reduced to intervals of a week after the first four to six treatments.

The iontophoresis method using methacholine may also be applied to the treatment of *ulcers, Raynaud's disease,* and *scleroderma.* Ten or more treatments may be necessary to secure improvement in Raynaud's disease and scleroderma. In *varicose, indolent* and *gangrenous ulcers,* treatment may be given daily at the start to promote granulation of the tissue and then reduced after the first few treatments to two or three times a week. Treatment by ion transfer (iontophoresis) should be carried out by one who has had special training. During these treatments the patient should be covered and protected from drafts and should remain quiet and warm for thirty minutes after each treatment.

Precautions: (1) The drug should never be administered intravenously for fear of cardiac arrest; (2) bronchial asthma, hyperthyroidism, coronary occlusion, and other severe illness are contraindications; (3) recumbence is advised during injection; (4) administration by iontophoresis requires special skill; (5) therapy should be stopped on appearance of grave side-reactions.

PREPARATIONS

Methacholine Chloride, *Methacholinae Chloridum,* U.S.P. (Acetyl-β-methylcholine chloride). $C_7H_{16}ClO_2N$. *Dosage:* Oral, 0.2 Gm. (3 grains); parenteral, 10 mg. (⅙ grain) (U.S.P.). By ion transfer, a 0.2 to 0.5 per cent solution of the drug in distilled water.

Methacholine Chloride Capsules, *Capsulae Methacholinae Chloridi,* U.S.P. *Dosage:* 0.2 Gm. of methacholine chloride, usually available in capsules containing that amount.

Methacholine Chloride Injection, *Injectio Methacholinae Chloridi,* U.S.P. *Dosage:* Parenteral, 10 mg. methacholine chloride, usually available in ampuls containing 10 mg. in 1 cc. The drug should never be administered intravenously.

Carbachol (Carbamylcholine Chloride)

Carbachol was introduced into threapeutics as a substitute for acetylcholine. The drug is available for clinical use in the form of its chloride salt.

Carbachol is a powerful parasympathomimetic agent more stable than methacholine chloride, but possessing nicotinic actions not shared by the latter. It exerts a more predominant action on the gastrointestinal tract. It has been used mainly in the control of *peripheral vascular disease* and *postoperative urinary retention.* In postoperative distention beneficial effects are due to stimulation of peristalsis by increasing intestinal tone. In urinary retention the drug increases bladder contraction and relaxation of the trigone and sphincter. It gives effective relief in the pain of peripheral vascular disease, and by subcutaneous injection its effects outlast those of methacholine.

Sinus Tachycardia.—Carbachol is useful in the treatment of this condition. Stimulation of vagus by parasympathomimetic drugs frequently brings about the arrest of attacks when carotid pressure is ineffective.

It does not, however, affect the heart rate of the tachycardia if due to organic disease.

Eye Diseases.—Locally in the eye, carbachol is a powerful miotic, causing marked contraction of the pupil, loss of accommodation through spasm of the ciliary muscle, and reduction of intraocular tension. Because of its toxicity it is seldom used in the treatment of glaucoma except when the eye does not respond to other miotic drugs. In glaucoma a 1.5 per cent solution is employed. Zephiran, 0.03 per cent, is added to the aqueous solution to promote penetration of the cornea.

The oral use of carbachol gives less dependable action, hence administration by injection is indicated.

PREPARATIONS

Carbachol, *Carbacholum*, U.S.P. (Carbamylcholine Chloride). $NH_2CO.O.CH_2CH_2.N(CH_3)_3.Cl$. *Dosage:* Oral, 2 mg. ($\frac{1}{30}$ grain). Subcutaneous, 0.25 mg. ($\frac{1}{240}$ grain).

Carbachol Injection, *Injectio Carbacholi*, U.S.P. *Caution: This preparation should not be injected intravenously. Dosage:* Subcutaneous, 0.25 mg. of carbachol (U.S.P.), usually available in ampuls each containing 0.25 mg. in 1 cc.

Carbachol Tablets, *Tabellae Carbacholi*, U.S.P. *Dosage:* 2 mg. of carbachol (U.S.P.) usually available in tablets which contain that amount of the drug.

Di-isopropyl Fluorophosphate ("DFP")

A new series of parasympathomimetic drugs, the fluorophosphates were developed in the course of studies on toxic substances in warfare. "DFP" destroys cholinesterase irreversibly, in contrast to the reversible inhibition of physostigmine and neostigmine. The effects last until cholinesterase is again built up in sufficient quantity.

This drug relieves muscle weakness of myasthenia gravis less completely but more persistently than neostigmine (Comroe, Todd, et al., 1946). It is too toxic, however, to be of much value in this condition. It relieves glaucoma, and is often more effective than physostigmine. Undesirable effects are visual blurring, eyeache, spasm of accommodation, and pericorneal congestion.

Choline

Choline (trimethyl-oxyethyl-ammonium hydroxide) occurs as a constituent of lecithin which is found in animal and vegetable tissues. It no doubt exists in combination, but is freed by putrefaction. It is not liberated by the action of pepsin and trypsin.

Like pilocarpine and muscarine, choline stimulates the peripheral ends of the autonomic nerves. Due to this action it causes an increase in various secretions, especially those of the salivary glands. It also causes a slowing of the pulse, miosis, and increased peristalsis. It depresses the respiratory center and lowers the blood pressure by causing vascular dilatation. Choline causes a tissue destruction somewhat similar to that caused by x-ray treatment. The chloride has been used with some success in ileus. Choline borate and choline chloride are on the market for intravenous use.

Arecoline

Arecoline ($C_8H_{13}NO_2$), one of the alkaloids contained in betel nut (*Areca catechu*), resembles pilocarpine in its action, but is more power-

ful, exerting a greater action on the central nervous system. It produces marked bronchial constriction by peripheral action, which is overcome by atropine and adrenalin. Arecoline has been suggested in the treatment of tapeworm infections. Arecoline, which causes stimulation of peristalsis, may be used as an antidote for mushroom poisoning of the muscarine type. It is used in veterinary medicine in the treatment of gastrointestinal disturbances.

Muscarine

Muscarine is chemically related to choline and may be produced artificially by gently heating choline platino-chloride with strong nitric acid. Muscarine resembles pilocarpine in its physiological action, and is antagonistic to atropine. It increases the secretions (sweat, salivary, and lacrimal), contracts the pupil, slows the pulse, and causes motor weakness. Small doses cause a reduction in the pulse rate by stimulation of the vagus nerve, while large doses may cause diastolic arrest of the heart. There is a stimulation of the muscles of the bladder, intestines, and spleen.

Muscarine is an alkaloid contained in the mushroom, *Amanita muscaria,* and to a less extent in some of the other species. The symptoms of muscarine poisoning, which are similar to those of pilocarpine poisoning, are first abdominal pain, vomiting, and diarrhea. Later suppression of urine, due to nephritis, and jaundice occur. Other symptoms include mental confusion, dizziness, sweating, slow pulse, and convulsions. *Treatment:* Remove poison by gastric and colonic lavage, sweating, and by intravenous injection of saline solutions. Atropine (1 mg.) subcutaneously is the physiologic antidote. Supportive measures with caffeine, camphor, etc., may be indicated.

PARASYMPATHOLYTIC DRUGS (INHIBITORY)

Atropine and Belladonna Group

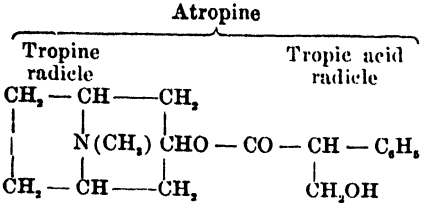
Alkaloids	*Crude Drug*
Atropine	*Atropa belladonna*
Scopolamine (Hyoscine)	*Scopolia atropoides*
Hyoscyamine	*Hyoscyamus niger*
Stramonium alkaloids	Synthetic
Homatropine	Synthetic
Eucatropine	Synthetic
Homatropine methylbromide	Synthetic
Eumydrine	Synthetic

The belladonna drugs are widely distributed in nature, especially in the Solanaceae plants. The synthetic derivatives are the result of attempts to secure atropine-like drugs which have more specific actions.

Atropine

Atropine, which is the chief alkaloid of *Atropa belladonna,* occurs in the form of white, amorphous crystals or powder and has a bitter taste. It is fairly insoluble in water (1:455) but soluble in alcohol (1:2). The leaves assay about 0.3 per cent of atropine; the roots, 0.45 per cent. Atropine is the tropeic ester of tropine, a pyridine compound; that

is, it consists of equal parts of levo-hyoscyamine and dextro-hyoscyamine. Atropine has the following structural formula:



Tropine is a pyridine compound closely related to ecgonine, a constituent of cocaine. Since the dextroform is practically inactive in the body, the action of atropine is due to the levo-hyoscyamine half.

Pharmacological Action.—Atropine and its related alkaloids depress the receptive substance of structures innervated by the parasympathetic nervous system. In larger doses they also have a depressant action on autonomic ganglia. The parasympathetic effect is not due to suppression of acetylcholine, but to failure of liberated acetylcholine to stimulate the atropinized cell. The atropine alkaloids possess stimulant, narcotic, anodyne, antispasmodic, mydriatic, rubefacient, anhydrotic, and antigalactagogic action.

Absorption and Excretion.—Atropine is rapidly absorbed from mucous membranes. Ointments and belladonna plasters are slowly absorbed by the intact skin. Elimination is rapid; a dose usually is completely excreted largely in the urine in thirty-six hours. A certain tolerance may be established toward atropine, and cumulative symptoms are said to occur.

Local Action: Action on the Skin.—Atropine is practically nonirritating; however, when applied locally in sufficient concentration, it depresses sensory and motor nerve endings, involuntary muscle tissue and also glandular tissue. It acts as an anodyne when applied to the skin as a belladonna plaster or as the liniment. It has similar action when applied to mucous membranes in the form of belladonna ointments and suppositories.

Action on the Eye: Mydriasis.—Atropine causes paralysis of the sphincter muscle of the iris and ciliary muscle of the lens; thus dilatation of the pupil (mydriasis) and paralysis of accommodation (cycloplegia) occur. The intraocular pressure tends to rise, possibly by pressing the iris into the crucial angle of the eye, resulting in hindering lymphatic drainage. This is true of most mydriatics (except cocaine) but especially so with atropine, due to its long action. None of these effects is seen in the bird's eyes, because their irides are made of striated muscle. Atropine acts on the eye following both systemic and local administration, but local administration is preferred.

The following table shows the strength usually employed for ophthalmoscopic examination and the ordinary duration of their actions (Sollmann, 1948).

Action on Secretions.—Atropine and related alkaloids arrest all secretions that depend on central innervation, such as sweat, saliva, tears, mucus, gastric juice, and ordinary pancreatic secretions. The secretion of hydrochloric acid is more affected than the secretion of pepsin (Riegel). This action is due to a paralysis of the secretory fibers in the vagus. The action of the drug prevents sweating whether it has been produced by pilocarpine, heat, tuberculosis, or aspirin. This

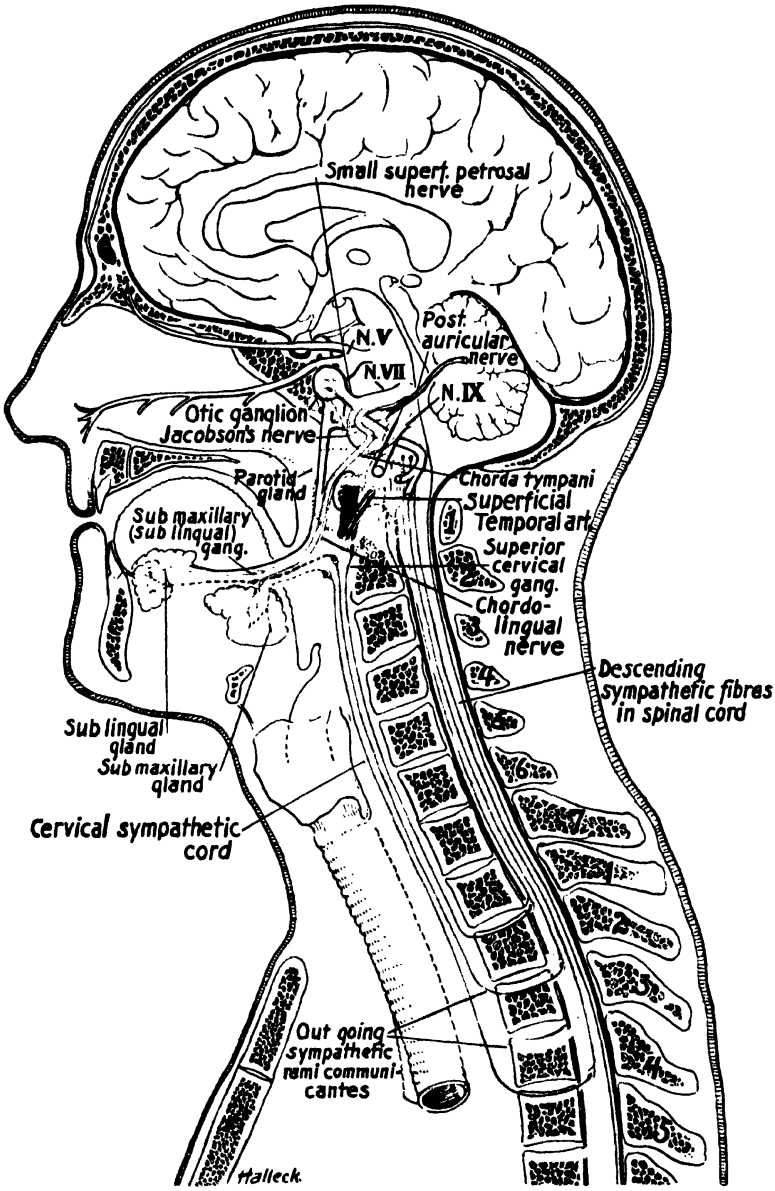


Fig. 10.—Schematic representation of the general plan of distribution of the nerves from the medullary centers to the salivary glands. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

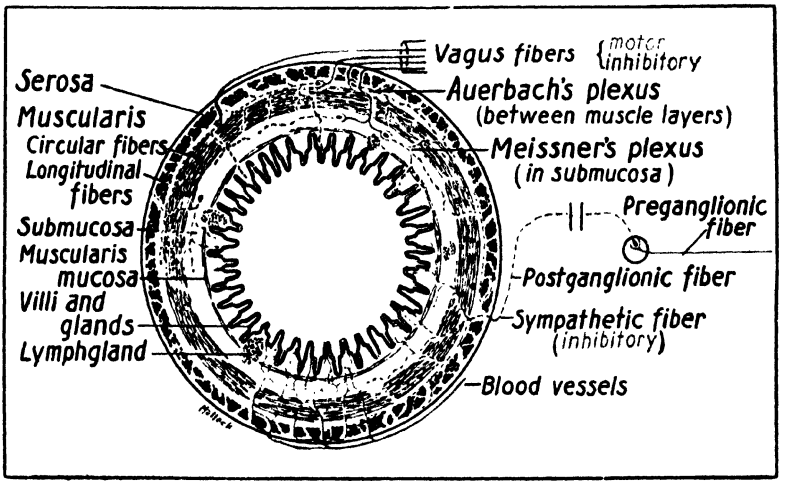


Fig. 11.—Diagrammatic cross section of the intestine (small) to show the manner of its innervation. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

TABLE XV

DRUG	PERCENTAGE USED	MYDRIASIS		CYCLOPLEGIA	
		ACTION COMPLETE (HOURS)	RECOVERY COMPLETE (DAYS)	PARALYSIS COMPLETE (HOURS)	RECOVERY COMPLETE (DAYS)
Atropine	1	½	5 to 7	2	3 to 4
Scopolamine	⅕	½	5	1	3
Eumydrine	1 to 5	½	2	1	2
Homatropine	2	½	1 to ½	1	1
Eucatropine	5 to 10	1	1		

action also seems to be on the nerve endings. Since the sweat glands are innervated by the sympathetic system, and the action of atropine is usually on the parasympathetic system, this action on the nerves of the sweat glands is a notable exception to the rule.

The amount of secretion of the *mammary gland* is not materially lessened by atropine, presumably because of the absence of secretory nerves. *Urinary secretion* is little influenced by atropine, as the kidneys are not controlled by secretory nerves. Lymph secretion also is not influenced by atropine. *Secretin*, the specific hormone of the pancreas (originating from the mucosa of the duodenum and jejunum), still causes a secretion after atropine, showing that the gland cells are still capable of functioning. The rate of change of *glycogen* into sugar is not influenced by atropine.

There is apparently little action on *bile secretion*. On this statement there is some difference of opinion. (Fig. 10.) The action is localized in the myoneural junction and is antagonistic to pilocarpine action.

Action on Involuntary Muscles.—Small doses of atropine increase intestinal peristalsis slightly, probably by depressing the inhibitory (splanchnic) nerve endings in the intestinal wall. Full therapeutic doses depress involuntary muscle directly.

Action on Stomach and Intestine.—Atropine in large doses depresses the parasympathetic nerves to the bowel (vagi and pelvic nerves), thus decreasing the tone and motility. Therapeutic doses, however, check excessive peristalsis caused by drugs (pilocarpine, etc.) or irritant cathartics. Therapeutic doses are effective in depressing spasm but have little effect on the normal gut. For a diagrammatic cross section of the intestine see Fig. 11.

It must be remembered that there is not a delicate balance between the vagi and splanchnics, and a depression of one does not necessarily result in the dominance of the other. For example, stimulation of either system may result in hypertonicity, depending on existing tonicity of the stomach.

Action on Spleen, Uterus, and Bladder.—The movements of these organs are lessened by atropine; however, very small doses may have a slight tendency to stimulate this activity.

Action on Nervous System.—Atropine in therapeutic doses has little effect on the brain and spinal cord; it does depress certain nerve-endings, especially those of the heart and secretory organs and certain involuntary muscles, with definite effects. Toxic doses stimulate the cerebrum, producing incoherent speech, laughter, and nervousness. This condition may be followed by a type of delirium known as the "belladonna jag," which may pass into maniacal excitement

before passing over to cerebral depression, characterized by drowsiness, stupor, and coma.

Action on Temperature.—Atropine causes a rise in temperature by arresting the action of the sweat glands and by stimulation of the heat regulatory center. Increased metabolism, however, is not a cause of the rise in temperature.

Action on Circulation.—Therapeutic doses of atropine depress the vagus and stimulate the vasomotor center and to a slight degree the cardiac muscle. This results in an increase of pulse rate and a rise in blood pressure. (Fig. 12.) In man, 1 mg. of atropine hypodermically may double the pulse rate in about twenty minutes. This effect usually lasts less than an hour. Toxic doses depress the circulation and cause a scarlet flushing of the skin affecting first the face and neck and then the chest. This phenomenon may occur even with therapeutic doses; it is due to dilatation of the cutaneous vessels. The action is believed to be central, since cutting of the sympathetic prevents it.

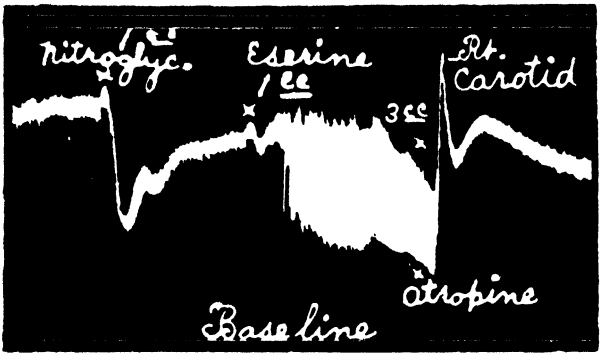


Fig. 12.—Blood pressure tracing from a dog showing the fall caused by nitroglycerin, the marked (vagus ending) slowing caused by eserine, and the following rise in pressure and acceleration of the heartbeat caused by atropine. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

Respiration.—Therapeutic doses of atropine stimulate the respiratory center, causing rapid and deep breathing. Toxic doses depress the center, causing asphyxia. This stimulation of respiration may be due to bronchial dilatation and also to increase of metabolism.

Action on Bronchial Muscles.—The bronchioles are innervated by the vagi which carry mainly constrictor fibers and a few dilator fibers. Atropine dilates the bronchioles; this effect is due to paralysis of the terminals of the motor nerves distributed to these muscles.

Toxicology.—Atropine poisoning may occur from overdosage by ophthalmologists, from ointments, or from ingesting the alkaloid or any of the crude drugs containing it. The liability to poisoning is greatest when the drug is administered hypodermically. The early symptoms of poisoning are dryness of the mouth and throat, thirst, dizziness, and dilated pupils. The stimulation stage is characterized by great thirst, burning of the throat, dysphagia, and flushed skin. The temperature and blood pressure rise. Delirium may occur, generally with noisy, disconnected talk and hallucinations, occasionally

with violent motor excitement and even convulsions. Collapse may follow the period of stimulation, which is characterized by low blood pressure, shallow respiration, and coldness of extremities; death usually results from respiratory failure. The symptoms are very violent but the prognosis is good, because the drug is rapidly excreted.

TABLE XVI

SUMMARY OF ATROPINE ACTION

(Typical Parasympathetic Depressant)

EFFECTS	USES	TOXIC SYMPTOMS
Dilates pupils, paralyzes accommodation.	Mydriatic, cycloplegic, anodyne.	Dilated pupils, dimness of vision.
Suppresses secretions of nose, mouth, and throat.	To treat coryza, rhinitis, salivation.	Dry mouth, difficult swallowing, hoarseness.
Dilates blood vessels of face and neck.		Flushed face and neck.
Dilates bronchi and suppresses secretions.	Treat bronchial asthma, spasms, pneumonia, hiccup, and pertussis.	Rapid, deep respiration, slow shallow breathing.
Accelerates heart.	Cardiac stimulant. Vagus bradycardia. Partial heart block from digitalis.	Tachycardia. High blood pressure.
Suppresses peristalsis and secretions of the stomach.	To treat gastric ulcers, gastrotetany, pyloric spasm, etc.	
Suppresses peristalsis and secretions of large and small intestine.	To treat spastic constipation. Antidote for pilocarpine in gut.	
Relaxes ducts and tubes.	Anodyne in renal and gallstone colic.	
Checks pancreatic and bile secretion. Inhibits tone of smooth muscles and the secretion of bladder, rectum, etc.	To counteract irritable bladder and urethra, as an anaphrodisiac.	
Suppresses sweating.	Suppresses sweating, e.g., tuberculosis.	Elevated temperature.

The *fatal dose* varies from 0.01 to 0.1 gram, death occurring usually within twenty-four hours. Kobert states that 88.4 per cent of all patients with atropine poisoning recover. Peterson, Haines, and Webster report 973 cases of atropine poisoning with 92 fatalities. *Autopsy findings* resemble those of asphyxia.

TREATMENT.—First empty the stomach with stomach tube, or by an emetic, such as apomorphine, 0.006 gram (1/10 grain), hypodermically.

If the case is not in an early stage it may be well to administer zinc sulfate, 2 grams (½ drachm) orally, or mustard, 8 grams (2 drachms) in warm water. Pilocarpine or physostigmine may be administered in the early stages; however, since the danger of atropine lies in its central action, the use of pilocarpine, etc., is of little value, as it acts peripherally. Delirium may be quieted by an ice bag over the head; morphine, 0.016 gram (¼ grain), is recommended. During the stage of depression stimulants, such as caffeine with sodium benzoate, strychnine, digitalin, etc., are indicated. Artificial respiration and intravenous infusion of saline may be of great assistance.

Therapeutic Uses.—Atropine and the related alkaloids are used especially as mydriatics and cycloplegics, to suppress secretions as in gastric hyperacidity, and to quicken the heart, regulate peristalsis, and lessen bronchial spasm. The tincture and the extract of belladonna and atropine sulfate are commonly taken internally, the tincture being used for solutions, and the extract or atropine sulfate is usually administered as pills or capsules.

Treatment of Eye Conditions.—In ophthalmology atropine is employed locally as a therapeutic agent, and also as an aid in diagnosis. It is used as follows: (1) to dilate the pupil in order to facilitate examination; (2) to paralyze accommodation, so that the refractive condition of the eye can be ascertained; (3) to rest the eye in inflammatory conditions by paralyzing its muscles, and (4) to aid in preventing and breaking up adhesions.

Mydriasis may be produced by instilling in the eye a couple of drops of 1 per cent atropine sulfate, which causes complete dilatation in about twenty minutes and complete loss of accommodation in one and one-half hours. The effects of the dilatation of the pupil may extend over several days, while the loss of accommodation may last one or two weeks. A weaker solution may be used to cause dilatation, without paralysis of accommodation.

Superficial Inflammation of the Eye.—Dilute solutions of atropine (0.1 to 0.4 per cent) instilled in the eyelids relieve pain, tenderness, and photophobia. A 0.1 per cent solution two to three times daily will relieve the pain and photophobia of *corneal ulcers* and *phlyctenular keratitis*. Atropine (0.5 to 1.0 per cent solutions) may be employed to produce constant dilatation of the pupil and thus prevent the formation of *synechiae*, a condition often associated with syphilitic iritis. Atropine will relieve the photophobia of *conjunctivitis*.

Repeated use of atropine may cause systemic poisoning. Infants may develop a fever from its administration. Toxic symptoms may be prevented by compression of the inner canthus of the eye. The intraocular pressure should be tested before the use of atropine. Atropine mydriasis may be overcome by physostigmine (1 minim of 0.2 per cent solution) several times daily.

Spasmodic Conditions.—Pertussis.—Atropine is effective in the spasmodic stage and in those cases characterized by profuse bronchial secre-

For pertussis:

℞

Belladonna Tincture	4.00 cc.	(f3j)
Alum	4.00 Gm.	(3j)
Tolu Balsam Tincture	30.00 cc.	(f3j)
Distilled Water q.s. ad	90.00 cc.	(f3iij)

M. Sig.: Give teaspoonful every three hours while awake (for child).

tion. Administer the tincture of belladonna in doses of 0.2 to 0.3 cc. (3 to 5 minims) every three to four hours, stopping with the first sign of dilatation of pupils or excessive dryness of the throat.

Bronchial Asthma.—Duke states: "Drugs of the atropine series are time-honored remedies in the treatment of asthma." During attacks of asthma, due largely to reflex spasm and narrowing of the bronchioles, atropine gives relief by paralyzing the motor endings of the vagus, thus relaxing the spasm. Atropine may be injected hypodermically in doses of 0.0005 to 0.00065 gram (1/120 to 1/100 grain). Clinically it cannot be relied upon in severe attacks.

The burning of stramonium leaves (stramonium leaves two parts, potassium nitrate one part, powdered anise one part) is an old remedy for mild attacks of asthma. The alkaloid and the nitrite formed from the nitrate relieve smooth muscle spasm. Atropine is of no value in cardiac asthma, as the moisture involved is not of secretory origin.

Enuresis.—Belladonna gives relief in cases caused by a relaxed condition of the vesical mucous membrane and by irritated conditions of the vesical mucous membrane. Treatment consists in beginning with a therapeutic dose on retiring and continuing use of the drug for several weeks, with diminishing doses and an occasional rest of one to three days during which no drug is given.

Hepatic, Intestinal, Uterine, and Renal Colic.—These conditions may be aided by atropine. The drug paralyzes the innervation of smooth muscle, and relaxes the obstructive spasm which prevents calculi or urine from free passage. Atropine, 1 mg. (1/60 grain), is indicated hypodermically. The drug may be combined with morphine, 15 mg. (¼ grain). Atropine prevents the morphine-induced muscle spasm.

For dysuria in treatment of cystitis:

℞

Sodium Citrate	24.00 Gm.	(℥vj)
Sodium Bromide	15.00 Gm.	(℥ss)
Belladonna Tincture	8.00 Gm.	(f℥ij)
Peppermint Water q.s. ad	90.00 cc.	(f℥iij)

M. Sig.: Teaspoonful in water every three hours as required.

In *pylorospasm,* atropine, 0.0005 gram (1/120 grain), often gives complete relief; however, the drug may fail to give relief. Infants are relatively insensitive to it; doses of 0.8 to 2.4 mg. (1/75 to 1/25 grain) may be administered with no side reactions.

Neuralgia.—Trigeminal neuralgia and sciatica often respond to atropine. For sciatic neuralgia, 0.00065 to 0.0011 gram (1/100 to 1/60 grain) of atropine may be injected intramuscularly near the nerve. In trigeminal neuralgia a solution of the drug may be administered externally.

Dysmenorrhea.—Many physicians use atropine with striking results in the treatment of this condition. Administer 0.0006 gram (1/100 grain) three times daily, beginning two days before menstruation and continue for two days after the onset.

In *myasthenia gravis* the usual method of treatment has been to give from 3 to 5 cc. of a 1:2,000 solution of neostigmine, combined with 0.0006 gram (1/100 grain) of atropine sulfate, intramuscularly once daily.

Skin Diseases.—Prurigo, herpes zoster, erythema, eczema, dermatitis and many other skin conditions respond to atropine. In chronic urticaria administer 0.01 to 0.02 gram (1/6 to 1/3 grain) of extract of belladonna.

For most painful and congested conditions apply atropine, a 1 per cent solution of the sulfate, externally.

Diseases of the Alimentary Tract.—Habitual constipation may be relieved by 0.01 to 0.03 gram (⅙ to ½ grain) of the extract in a pill, administered on retiring.

For chronic constipation:

℞

Belladonna Extract	24.00 Gm.	(3vj)
Nux Vomica Extract	0.26 Gm.	(gr.iv)
Aloin	0.26 Gm.	(gr.iv)
Cascara Sagrada Extract	4.00 Gm.	(3j)

M. ft. pil. No. xxiv.

Sig.: One at bedtime.

Gastric hyperacidity, when unrelieved by other means, may respond to atropine (0.0005 Gm.) when it is added to the antacid employed. The pain of gastric ulcer may be relieved by the administration of atropine.

For pain of gastric ulcer:

℞

Atropine Sulfate	0.013 Gm.	(gr.⅕)
Zinc Sulfate	2.00 Gm.	(gr.xxx)
Distilled Water	30.00 cc.	(f3j)

M. Sig.: Three drops three times daily.

In *hemorrhage* from peptic ulcer Bolton (1936) advises the use of atropine sulfate 0.0006 to 0.0012 gram (1/100 to 1/50 grain) hypodermically to dilate the pylorus.

Premedication.—Atropine, 0.00085 to 0.00065 gram (1/75 to 1/100 grain), may be given intramuscularly, subcutaneously, or intravenously before the anesthetic. The drug aids in diminishing secretions and by abolishing cardiac inhibition by anesthetic agents.

To Suppress Secretions.—Atropine is rarely used in therapeutics to suppress sweating and salivation; however, the night sweats of phthisis may be checked by subcutaneous injections of atropine, 0.0011 gram (1/60 grain). The copious sweating induced by pilocarpine, alcohol, etc., may be suppressed by atropine.

As Antidote.—Atropine, in doses of 0.0016 gram (1/40 grain), is recommended for opium poisoning. It is also effective in pilocarpine or physostigmine poisoning. In lead poisoning it may be employed in a dose of 0.0006 gram (1/100 grain). The colicky pains of food poisoning may be controlled by the administration, hypodermically, of dilaudid combined with atropine sulfate 0.0005 gram (1/120 grain). Atropine sulfate, 0.0012 gram (1/50 grain) hypodermically, is indicated to control toxic action of mecholin.

Cardiac Disorders.—Atropine has few valid uses in heart disorders. *Partial Heart Block:* Atropine may be used in partial heart block, presumably by its inhibitory action on the vagus. The dose ranges from 0.5 to 1 mg. In complete heart block large doses (3 to 5 mg.) may be given, but success is rare. *Vagus Bradycardia:* Atropine (0.5 to 1 mg.) is effective in treating such conditions caused by disease, or from overdoses of digitalis, pilocarpine, physostigmine, acetylcholine, etc. *Cardiac Irregularities:* Heart irregularities may be abolished by small doses of atropine. *Diagnostic Use:* Atropine is used to diagnose whether or not cardiac slowing is due to vagus stimulation. Administer 0.5 to 1 mg.

PREPARATIONS

Atropine, *Atropina*, U.S.P., B.P. *Dosage:* 0.4 mg. (1/150 grain).
Atropine Sulfate, *Atropinae Sulfas*, U.S.P., B.P. *Dosage:* 0.5 mg. (1/120 grain).
Atropine Sulfate Tablets, *Tabellae Atropinae Sulfatis*, U.S.P. The usual sizes contain 0.12 mg., 0.3 mg., 0.4 mg., 0.5 mg., 0.6 mg., and 1.2 mg.
Belladonna Leaf, *Belladonnae Folium*, U.S.P., B.P., yields about 0.3 per cent of alkaloids. *Dosage:* 0.06 Gm. (1 grain).
Belladonna Root, *Belladonnae Radix*, N.F., B.P., yields about 0.45 per cent of alkaloids. *Dosage:* 45 mg. (¾ grain).
Belladonna Extract, *Extractum Belladonnae*, U.S.P., Belladonna extract yields about 1.25 per cent of alkaloids. *Dosage:* 0.015 Gm. (¼ grain). *Extractum Belladonnae Sicum*, B.P. *Dosage:* 0.015-0.06 Gm. (¼ to 1 grain).
Belladonna Tincture, *Tinctura Belladonnae*, U.S.P., B.P. Belladonna leaf (10%) yields about 0.03 per cent of alkaloids in alcohol. *Dosage:* 0.6 cc. (10 minims).
Belladonna Plaster, *Emplastrum Belladonnae*, N.F., B.P. It contains extract of belladonna and yields about 0.27 per cent of alkaloids.
Belladonna Root Fluidextract, *Fluidextractum Belladonnae Radicis*, N.F. Belladonna root (100%) yields about 0.45 per cent of alkaloids. *Dosage:* 0.05 cc. (¾ minim).
Belladonna Ointment, *Unguentum Belladonnae*, U.S.P. Pilular extract of belladonna (10%) in diluted alcohol, and yellow ointment.

Scopolamine (Hyoscine)

Scopolamine, or hyoscine ($C_{17}H_{21}NO_4$), is an alkaloid obtained from various plants of the Solanaceae family, including *Atropa belladonna*, *Datura stramonium*, *Hyoscyamus niger*, and *Scopolia atropoides*. Officially, that is from the standpoint of the U.S.P., scopolamine and hyoscine are identical; however, scopolamine is levo-rotatory and hyoscine may be levo-rotatory to inactive (equal amounts of dextro- and levo-) molecules. Scopolamine, being levo-rotatory, is thus more unstable than atropine. Its purest samples exhibit a great variation in action and toxicity.

Pharmacological Action.—Scopolamine possesses sedative, antispasmodic, anodyne, and mydriatic action. It resembles atropine in its influence on nerve endings, but differs from it in having a sedative, instead of a stimulating, effect on the brain.

Action on Central Nervous System.—Scopolamine produces a pronounced depression of the psychic and motor centers of the brain, produces a hypnotic effect, and, if the doses are large enough, narcosis. The motor centers are depressed easily and the subject becomes sluggish and soon falls asleep. Occasionally sleep is preceded by a short period of excitement. Large doses produce a depression of the spinal cord.

The peripheral effects of scopolamine, which are similar to those of atropine, consist of paralysis of the parasympathetic nerve endings. Sometimes slowing of the heart is noticed after scopolamine administration, which may be the result of motor inactivity or some impurity in the drug administered.

Circulation.—Scopolamine, in therapeutic doses, rarely causes acceleration of the heart. It rarely stimulates the vasomotor center; however, toxic doses depress this center, and this is followed by a corresponding fall in blood pressure.

Respiration.—Large doses depress respiration.

Eye.—Scopolamine (0.2 per cent solution) will dilate the pupil in ten to thirty minutes and induce paralysis of accommodation. The action is due to paralysis of the oculomotor nerve endings in the constrictor muscle and the ciliary muscle, respectively. The mydriatic effect of the drug passes off more rapidly than that of atropine; it lasts three to five days, while the power of accommodation returns in four to five days.

Secretions.—Secretions are inhibited as with atropine.

Toxicology.—Idiosyncrasies to scopolamine are common and it should be administered with care. The toxic symptoms and treatment are largely the same as for belladonna and its alkaloids. There is a greater tendency to the development of psychoses. Somnolence and dizziness may appear in ophthalmic use of the drug. The toxic dose ranges between 0.6 and 2 mg. (1/100 to 1/30 grain). Doses larger than therapeutic doses cause, in addition to dryness of the mouth, mydriasis, and dysphagia, such symptoms as ataxia, unconsciousness, delirium, muscular weakness, rapid pulse, noisy respiration, cold perspiration, and collapse.

TREATMENT.—If the drug has been taken orally, evacuate the stomach with stomach tube or emetics. Administer tannic acid or Lugol's solution orally before emptying the stomach. Pilocarpine, 0.016 gram (1/4 grain), or strychnine, 2 to 3 mg. (1/30 to 1/20 grain), may be administered. Strong hot coffee is indicated. In cases of delirium administer chloral hydrate in doses of 0.6 gram (10 grains). Administer digitalis, epinephrine, caffeine and ammonia preparations in circulatory depression. Artificial respiration and heat may be used.

Therapeutic Uses.—*As Sedative.*—Scopolamine, in doses of 0.2 mg. (1/300 grain), administered hypodermically, is indicated in *insomnia* due to mental or motor excitement. Combined with morphine it is effective in insomnia due to pain; it augments the activity of morphine and no ill effect is apparent with this drug combination.

In *delirium tremens* a hypodermic injection of scopolamine hydrobromide, 0.6 mg. (1/100 grain), with apomorphine hydrochloride, 3.0 mg. (1/20 grain), and strychnine sulfate, 2 mg. (1/30 grain), is recommended. In the tremor of *paralysis agitans,* scopolamine may be administered hypodermically in daily doses of 0.25 to 0.5 mg. (1/240 to 1/120 grain). It has also been recommended for *senile* and *alcoholic tremor.*

Scopolamine is effective in the treatment of *acute maniacal states.* At the first intimation of hyperactivity the patient is given a cathartic, followed by 0.6 to 0.8 mg. (1/100 to 1/75 grain) of scopolamine hydrobromide. The effect is rapid and lasts for several hours.

In Ophthalmology.—In *rheumatic* or *syphilitic iritis* scopolamine is, by instillation, sometimes preferred over atropine. It apparently does not increase intraocular tension. This drug has been used successfully in the treatment of other inflammatory infections of the eye, such as *iritis, uveitis,* and *sympathetic ophthalmitis.*

Scopolamine administered in two instillations of a drop each of a 0.06 gram (1 grain) to 30 cc. (1 ounce) solution of the hydrobromide at an interval of thirty minutes produces complete *mydriasis* and *cycloplegia* in less than thirty minutes. The mydriasis and paralysis of accommodation pass off in from two to four days. Pressure over the inner canthus prevents drainage into the nasal cavities and minimizes the chances of constitutional effects.

Premedication in Anesthesia.—Doses of from 0.01 to 0.02 Gm. (1/6 to 1/3 grain) of morphine and 0.5 to 1.0 mg. (1/120 to 1/60 grain) of

scopolamine hydrobromide, given hypodermically two hours before inhalation anesthesia, are considered an excellent form of premedication. Such a procedure quiets the patient and permits an anesthesia to be administered with ease and without struggling. The air-ways are not obstructed by secretions and postoperative discomfort and danger are at a minimum. This type of premedication is especially indicated in neurotic patients and in patients with pathology of the respiratory tract.

Morphine and scopolamine also furnish a desirable type of premedication for local and spinal anesthesia. They quiet the patient, allay fear and apprehension, and reduce any shock to the nervous system that might attend the operation.

Obstetrical Anesthesia.—Small doses of scopolamine and morphine have been used in labor to produce partial anesthesia or "twilight sleep." Doses of 0.0003 to 0.0005 Gm. are given and the narcotic effect is enhanced by small doses of morphine, 0.008 to 0.015 Gm. (⅛ to ¼ grain). The success of the procedure depends on its careful administration according to a technic that can hardly be described here with sufficient detail to be useful. Opinions as to the value of morphine-scopolamine administration in obstetrics vary. The disadvantages include prolongation of labor and narcotization of the baby. Adherents of the procedure assert that narcotization of the baby, if encountered, is the fault of the dosage and technic used in the procedure. Many agree that the method is of value for its psychic effect in neurotic primiparas in whom a long, painful labor is contraindicated.

Parkinson's Disease.—Scopolamine (0.3 to 0.6 mg.) intramuscularly relieves the rigidity and tremor of postencephalitic Parkinson's disease. The action is probably central since the efficacy of the atropine-like compounds in this disease is relative to their central-depressant action.

PREPARATION

Scopolamine Hydrobromide, *Scopolaminae Hydrobromidum*, U.S.P. *Dosage:* 0.5 mg. (1/120 grain). *Hyoscinae Hydrobromidum*, B.P. *Dosage:* 0.0003-0.0006 Gm. (1/200-1/100 grain).

Hyoscyamine

Hyoscyamine is found in *Hyoscyamus niger* in company with hyoscine (scopolamine) and traces of atropine. Hyoscyamus contains not less than 0.040 per cent of alkaloids. Hyoscyamine predominates in the older plants. It is a white crystalline, slightly soluble alkaloid, *l*-tropyltropeine, $CH_3.N.C_6H_{10}CH.O.CO.CH(C_6H_5)CH_2OH$, and when racemized with alkalies it forms atropine. It is never obtained pure since it is always mixed with atropine.

Pharmacological Action.—Hyoscyamus acts on the central nervous system like atropine, stimulating the respiratory and vasomotor centers in therapeutic doses. Large amounts, however, cause delirium followed by stupor. Peripherally the action is similar to, but more powerful than, that of atropine. The degree of the effect varies directly with the amount of levo-rotatory power of the sample used.

Toxicology.—The symptoms of poisoning are dryness of the throat, mydriasis, a feeling of fullness in the head, dizziness, acceleration of the pulse rate, muscular weakness, and delirium. Stupor and coma may follow.

Treatment.—Administer at once Lugol's solution or potassium permanganate and immediately following this use the stomach tube

or give an emetic. Pilocarpine hydrochloride, 0.015 gram (¼ grain), may be administered hypodermically. Delirium may be treated by morphine, 0.015 gram (¼ grain). Stimulants, such as hot coffee or strychnine sulfate, 0.003 gram (1/20 grain), may be used if indicated.

Therapeutic Uses.—Preparations of hyoscyamus or its alkaloid, hyoscyamine, are used as an antispasmodic anodyne, in mental disorders, colic, cough, etc. The tincture is the preparation of choice for fluid prescriptions. The powdered extract is commonly used, but the alkaloidal salt is rarely prescribed.

Sedative in Urinary and Bladder Conditions.—Hyoscyamus is an excellent sedative for the relief of pain in painful micturition in excessive bladder irritability as found in *cystitis, pyelitis,* and *urethritis.* Considerable relief is obtained in these conditions following the administration of tincture of hyoscyamus and potassium acetate.

For relief of pain in pyelitis and cystitis:

℞

Hyoscyamus Tincture	30.00 cc.	(f℥j)
Potassium Acetate	30.00 Gm.	(℥j)
Distilled Water q.s. ad	180.00 cc.	(f℥vj)

M. Sig.: Two teaspoonfuls in water after meals.

Hyoscyamus is an excellent sedative in the dry, hacking type of *cough* and in *whooping cough.* Powdered hyoscyamus is frequently a constituent of *asthma* powders or asthma cigarettes. The nervousness and insomnia following withdrawal of morphine or opium may be allayed by the use of hyoscyamus in combination with chloral hydrate and cannabis indica.

For treatment of cough:

℞

Codeine Sulfate	0.30 Gm.	(gr. v)
Hyoscyamus Tincture	12.00 cc.	(f℥iij)
Tolu Balsam Tincture	15.00 cc.	(f℥ss)
Distilled Water q.s. ad	90.00 cc.	(f℥iij)

M. Sig.: Teaspoonful every three hours.

Preparations

Hyoscyamus, *Hyoscyamus,* U.S.P., B.P. Leaves and tops, yielding not less than 0.04 per cent of alkaloids. *Dosage:* 0.2 Gm. (3 grains).

Hyoscyamus Extract, *Extractum Hyoscyami,* N.F. Yields about 0.15 per cent of alkaloids. *Dosage:* 0.05 Gm. (¾ grain).

Hyoscyamus Fluidextract, *Fluidextractum Hyoscyami,* N.F., yields 0.035 to 0.045 per cent of alkaloids of hyoscyamus. *Dosage:* 0.2 cc. (3 minims).

Hyoscyamus Tincture, *Tinctura Hyoscyami,* U.S.P. Hyoscyamus (10%) yields about 0.004 per cent of hyoscyamus alkaloids. *Dosage:* 2 cc. (30 minims). B.P., 2-4 ml. (30-60 min.).

Stramonium Alkaloids

Stramonium consists of the dried leaves and flowering tops of *Datura stramonium* (Jamestown weed, Jimson weed, thorn apple). Stramonium yields not less than 0.30 per cent of hyoscyamine and traces of scopolamine, but these amounts are not large enough to influence its physiological activity.

Pharmacological Action.—Stramonium and belladonna are practically identical in the symptoms of toxicity and in their general physiological actions. Stramonium has no advantage over atropine, but has acquired special reputé in the treatment of asthma. In poisonous doses the symptoms and treatment are like those given for belladonna and atropine.

Therapeutic Uses.—Stramonium is a favorite remedy in *spasmodic asthma.* Stramonium leaves may be smoked in a pipe or cigarette, or mixed with potassium nitrate and ignited in a saucer. The tincture is sometimes given by mouth, but is rarely prescribed. A good mixture for inhaling is one of three parts potassium nitrate, one and one-half parts of potassium chlorate, three parts of powdered stramonium leaves, and one part of ipecac. The following prescription is satisfactory:

℞

Sodium Nitrate	15.00 Gm. (℥ss)
Anise	15.00 Gm. (℥ss)
Stramonium	30.00 Gm. (℥j)

M. Sig.: Ignite a teaspoonful and inhale.

The stramonium tincture as well as the powdered leaf, has recently proved efficacious in alleviating the tremor of *paralysis agitans.* The ointment is used to relieve the pain and tenesmus caused by *hemorrhoids* and *fissures.* Stramonium is strongly recommended by Jones (1935) for the treatment of *Sydenham's chorea.*

Encephalitis Lethargica.—Powdered stramonium leaves (in capsules or pills) may be administered at one- or two-hour intervals. In the beginning give 1 to 2 grams (15 to 30 grains) distributed over the first day (24 hours). A maintenance dose of 0.5 gram (8 grains) may be given and be well tolerated for months.

Preparations

Stramonium, *Stramonium,* U.S.P., B.P. Leaves, containing not less than 0.25 per cent of alkaloids. *Dosage:* 0.075 Gm. (1¼ grains).

Stramonium Extract, *Extractum Stramonii,* U.S.P. One gram of extract represents about 4 Gm. of stramonium and yields about 1 per cent of stramonium alkaloids. *Dosage:* 0.02 Gm. (⅓ grain).

Stramonium Tincture, *Tinctura Stramonii,* U.S.P., Stramonium (10%), yielding about 0.025 per cent of stramonium alkaloids. *Dosage:* 0.75 cc. (12 minims). B.P., 0.3-2 ml. (5-30 min.).

Homatropine

Homatropine, a mydriatic alkaloid, $C_{16}H_{21}NO_3$, or tropine mandelate, is obtained by the condensation of tropine and mandelic acid. The hydrobromide is the only official salt. It occurs as white, small crystals, soluble in water (1:6).

Pharmacological Action.—Homatropine acts similarly to atropine but is much weaker. It rapidly dilates the pupils and paralyzes accommodation but the effects pass off in twenty-four to forty-eight hours, whereas the mydriasis of atropine lasts from ten to twelve days. Homatropine is much less toxic than atropine.

Therapeutic Uses.—Homatropine is used almost exclusively for mydriasis and to paralyze the muscles of accommodation for correcting anomalies in refraction. For *examination for refraction*

instill one drop of 1 per cent solution of homatropine in the eye every five or ten minutes for one and one-half hours. After thirty or forty minutes the examination can be made.

PREPARATIONS

Homatropine Hydrobromide, *Homatropinae Hydrobromidum*, U.S.P., B.P. *Dosage:* 0.5 mg. ($\frac{1}{120}$ grain), orally. May be used in 1 to 2 per cent aqueous solution.

Eucatropine, employed as Eucatropine Hydrochloride, $C_{17}H_{23}O_3N$, U.S.P., is used as a mydriatic and causes no paralysis of accommodation. Administer from 2 to 3 drops of 5 to 10 per cent solution. Maximal dilatation occurs in thirty minutes, and the iris returns to normal in two to three hours. It is useful as an aid in ophthalmoscopic examination in place of atropine, homatropine, etc.

Homatropine Methylbromide, N.F., $C_{17}H_{24}O_3NBr$, is proposed for use in the treatment of gastrointestinal spasm and hyperchlorhydria. It is less toxic and also less active than atropine. *Dosage:* One or two tablets (2.5 mg. per tablet) three times daily before meals; children and infants according to age.

Eumydrine (Methylatropine Nitrate). This substance is readily soluble in water. Its systemic actions are similar to atropine and may be substituted for it in the same dosage. Its toxicity is about one-fiftieth, and its mydriatic strength about one-tenth, that of atropine. Continued use may lead to tolerance.

References

Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 3, Baltimore, 1943, Williams & Wilkins Co.

Brown, G. L.: Transmission at Nerve Endings by Acetylcholine, Physiol. Rev. **17**: 486, 1937.

Cannon, W. B., and Rosenblueth, A.: Autonomic Neuro-Effector Systems, New York, 1937, The Macmillan Co.

Dale, H. H.: Chemical Transmission of Effects of Nerve Impulses, Brit. M. J. **1**: 835, 1934.

Dameshek, W. A., and Feinsilver, O.: Human Autonomic Pharmacology, J. A. M. A. **109**: 561, 1937.

Davis, L., and Pollock, L. J.: Role of the Autonomic Nervous System in the Production of Pain, J. A. M. A. **106**: 350, 1936.

Henderson, V. E., and Roepke, M. H.: Drugs Affecting Parasympathetic Nerves, Physiol. Rev. **17**: 373, 1937.

Jackson, D. E.: Essential Pharmacology of the Autonomic Nervous System, J. A. M. A. **106**: 345, 1936.

Kramer, D. W.: Peripheral Vascular Diseases, Philadelphia, 1948. F. A. Davis Co.

Kuntz, A.: Essential Anatomy of the Autonomic Nervous System, J. A. M. A. **106**: 345, 1936.

Loewi, O.: Problems Connected With the Principle of Humoral Transmission of Nerve Impulses, Proc Roy. Soc. **118**: 299-316, 1935.

Myerson, A.: Theories and Results of Autonomic Drug Administration, J. A. M. A. **110**: 101, 1938.

Parker, G. H.: Humoral Agents in Nervous Activity, London, 1932, Cambridge University Press.

Wechsler, I. S.: Chemical Neurology, ed. 5, Philadelphia, 1943, W. B. Saunders Co.

White, J. P., and Smithwick, R. H.: The Autonomic Nervous System, New York, 1942, The Macmillan Co.

Parasympathomimetic Drugs

Alles, G. A.: The Physiological Significance of Choline Derivatives, Physiol. Rev. **14**: 276, 1934.

Council on Pharmacy and Chemistry: Acetyl-Betamethyl-Choline, J. A. M. A. **117**: 800, 1941.

Fox, M. J., and Spankus, W. H.: The Value of Neostigmine in Acute Anterior Poliomyelitis, J. A. M. A. **128**: 720, 1945.

Leopold, I. H., and Comroe, J. H., Jr.: Use of Diisopropyl Fluorophosphate ("DFP") in Treatment of Glaucoma, Arch. Ophth. **36**: 1, 1946.

McGavack, T. H.: Acetyl-Betamethyl-Choline as a Therapeutic Agent, M. Clin. North America **24**: 819, 1940.

Soskin, S., Wachtel, H., and Hechter, O.: Prostigmine Methyl-sulfate for Delayed Menstruation; a Therapeutic Test for Early Pregnancy, J. A. M. A. **114**: 2090, 1940.

Starr, Isaac: Studies on the Action and Utility of Several Stable Derivatives of Choline, Tr. Ass. Chem. Phys. **51**: 326, 1936.

Starr, Isaac: Acetyl-Betamethyl-Choline IV. Further Studies of Its Action in Paroxysmal Tachycardia, etc., Am. J. M. Sc. **191**: 210, 1936.

Viets, H. R.: Myasthenia Gravis, J. A. M. A. **127**: 1089, 1945.

Waldman, S., and Moskowitz, S. N.: The Treatment of Attacks of Sinus Tachycardia With Prostigmine, Ann. Int. Med. **20**: 793, 1944.

Winkelstein, L. B.: Prostigmine Methylsulfate and Delayed Menstruation, Am. J. Obst. & Gynec. **44**: 231, 1942.

Parasympatholytic Drugs

Graham, D. P. D., and Gunn, J. A.: The Comparative Activities of Atropine, l-hyoscyamine, Hyoscine and Homatropine on Mammalian Smooth Muscle, Quart. J. Pharm. & Pharmacol. **17**: 88, 1944.

Henderson, V. E., and Sweeten, M. O.: The Effect of Atropine on the Gastrointestinal Canal and Its Glands, Am. J. Digest. Dis. **10**: 241, 1943.

Loman, J., Myerson, P. G., and Myerson, A.: Experimental Pharmacology of Post-encephalitic Parkinson's Disease, Arch. Neurol. & Psychiat. **47**: 399, 1942.

Martin, J. E.: Atropine Glaucoma, Brit. M. J. **1**: 631, 1943.

Wangeman, C. P., and Hawk, M. H.: The Effects of Morphine, Atropine, and Scopolamine on Human Subjects, Anesthesiology **3**: 24, 1942.

CHAPTER XIII

DRUGS ACTING ON THE PERIPHERAL NERVOUS SYSTEM

II. THE SYMPATHETIC NERVOUS SYSTEM; PARASYMPATHETIC AND SYMPATHETIC GANGLIA

SYMPATHOMIMETIC DRUGS

The sympathomimetic drugs in general are those agents which stimulate the terminations of the sympathetic nerves. They may well be subdivided into two groups: those which stimulate the effector mechanism directly, e.g., epinephrine, phenylephrine (neosynephrine), and kephrine; and another group which acts by preserving sympathin, probably by blocking the amine oxidase, e.g., ephedrine, amphetamine, propadrine, and paredrine.

Epinephrine

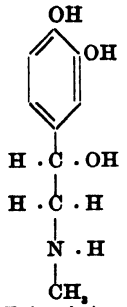
Epinephrine (adrenalin, suprarenin) is our most interesting drug because it is a hormone of the adrenal medulla and simulates so closely the effects of stimulation of the sympathetic nervous system. It is an animal alkaloid obtained commercially from the medullary part of the adrenal glands of sheep, cattle and hogs (0.1% of gland is epinephrine). It is also prepared synthetically. The natural epinephrine is levo-rotating, while synthetic epinephrine is optically inactive, but resolvable in the dextro- and levo- forms. Dextro-rotating epinephrine is almost inactive, the mixture of dextro- and levo- forms is about one-half as active physiologically as is natural (levo-) epinephrine. The levo-rotation product is the only one used in medicine.

The active principle of the adrenal gland was first isolated by Abel, in the form of a benzoyl compound, and was named epinephrine. A fine crystalline compound was isolated by Takamine and Aldrich in 1901 and named adrenalin. Stoltz (1906) synthesized epinephrine. Barger and Dale (1910) prepared an extensive series of similar sympathomimetic-acting drugs. Some of these are marketed as well as synthetic epinephrine.

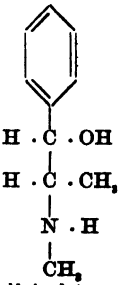
Epinephrine is methylaminoethanolcatechol. It has been prepared synthetically from catechol and is a derivative of parahydroxyphenyl ethyl amine. Epinephrine differs from other alkaloids in not being precipitated by alkaloidal reagents, and in being practically insoluble in alcohol. It is easily oxidized; it is, therefore, often dispensed with a reducing agent, alcohol, and the solvent is made acid.

Epinephrine, though related chemically to ephedrine, still has important differences in action. Epinephrine has increased action on structures whose sympathetic system is degenerated. This may be apparent in some patients following a sympathectomy. Another difference of importance is that cocaine sensitizes the sympathetic mechanism to epinephrine, and thus increases its action. This does not hold with ephedrine, probably because of the absence of the hydroxy-phenyl group in ephedrine.

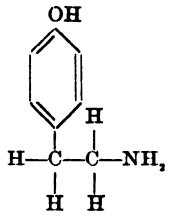
Pharmacological Action.—Epinephrine is a cardiac stimulant and vasoconstrictor. It acts by stimulating the "receptive substance" of



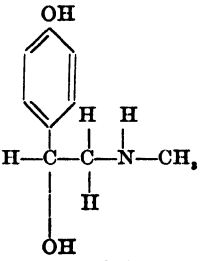
Epinephrine



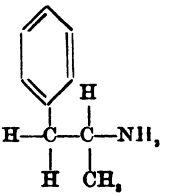
Ephedrine



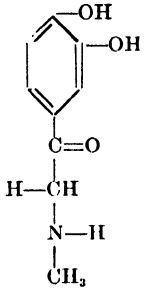
Tyramine



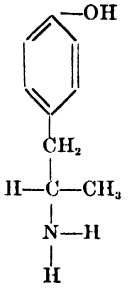
Neosynephrine



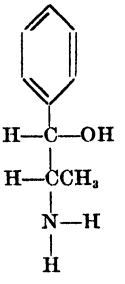
Amphetamine



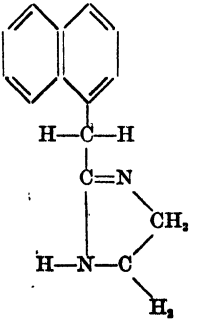
Kephrine



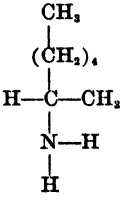
Paredrine



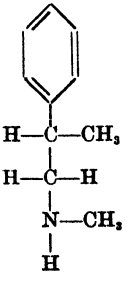
Propadrine



Nephazoline (Privine)



Tuamine



Vonedrine

the effector organs innervated by the peripheral sympathetic nerves. It produces all the phenomena of sympathetic nervous stimulation except mydriasis and sweating. Sweating, however, may occur with large doses. It is a true sympathomimetic amine. (Mimetic, Gr. *mimatikor,* to mimic or imitate.)

Epinephrine and pituitrin have certain actions in common. They both stimulate the uterine muscle and raise blood pressure by constricting vessels. They differ, however, in that pituitrin action is not on the sympathetic innervation of the structures acted upon, whereas epinephrine acts only upon structures receiving sympathetic innervation.

Ergotoxine or *ergotamine* annuls the excitatory (motor and secretory) responses of epinephrine or of sympathetic stimulation; but the inhibition effects, e.g., vasodilator, are not interfered with. The hyperglycemic response is negated by ergotoxine. *Apocodeine* is another drug which reverses some of the effects of epinephrine, whereas *cocaine* enhances its vasoconstrictor, cardiac, and pupillary reactions.

ABSORPTION AND EXCRETION.—Epinephrine is readily absorbed from mucous membranes. It is destroyed by digestive enzymes, thus is contraindicated by mouth. Its effects appear in five to fifteen minutes, when administered intramuscularly or subcutaneously, and at once when given by vein. The drug is rapidly destroyed in the body and rapidly excreted; its effects pass off in fifteen to thirty minutes.

LOCAL ACTION.—Epinephrine has no local effect upon the skin; but when applied to wounds or mucous membranes, or injected into tissues, it quickly constricts the vessels near the site of application. No drug known to medicine causes such complete vasoconstriction as epinephrine when applied locally; the effect lasts thirty minutes to two hours, while systemic action lasts about five minutes. Very small doses of the drug may cause vasodilatation which might explain the after congestion following an epinephrine spray.

It is an interesting fact that chance or necessity frequently brings about the practically simultaneous discovery of two substances, one or both of which would be sharply limited in usefulness without the other. The discovery of epinephrine has had a profound bearing upon the application of local anesthesia in surgery. Epinephrine produces constriction of the blood vessels, and when administered with a local anesthetic, it delays absorption, decreases toxicity, increases duration of anesthesia, and decreases hemorrhage. The abandonment of some local anesthetics, such as the eucaines, has been partially due to their incompatibility with epinephrine.

GENERAL METABOLISM.—Oxygen consumption is increased by from 20 to 40 per cent and carbon dioxide from 30 to 50 per cent. In man, the subcutaneous injections of 0.5 cc. of a 1:1,000 solution cause an increase in basal metabolic rate. The temperature rises (calorigenic action). The effect may be partly the result of hyperglycemia and partly due to direct stimulant action upon cellular oxidative processes. Definite circulatory and respiratory effects accompany the increased heat production.

CENTRAL ACTION.—The central effects of epinephrine are attributed largely, if not entirely, to secondary stimulation of the vagus and the respiratory center.

Respiration may become irregular during high blood pressure, and periods of strong and rapid breathing may alternate with apnea. The action may be due to high blood pressure rather than to direct action on the respiratory center.

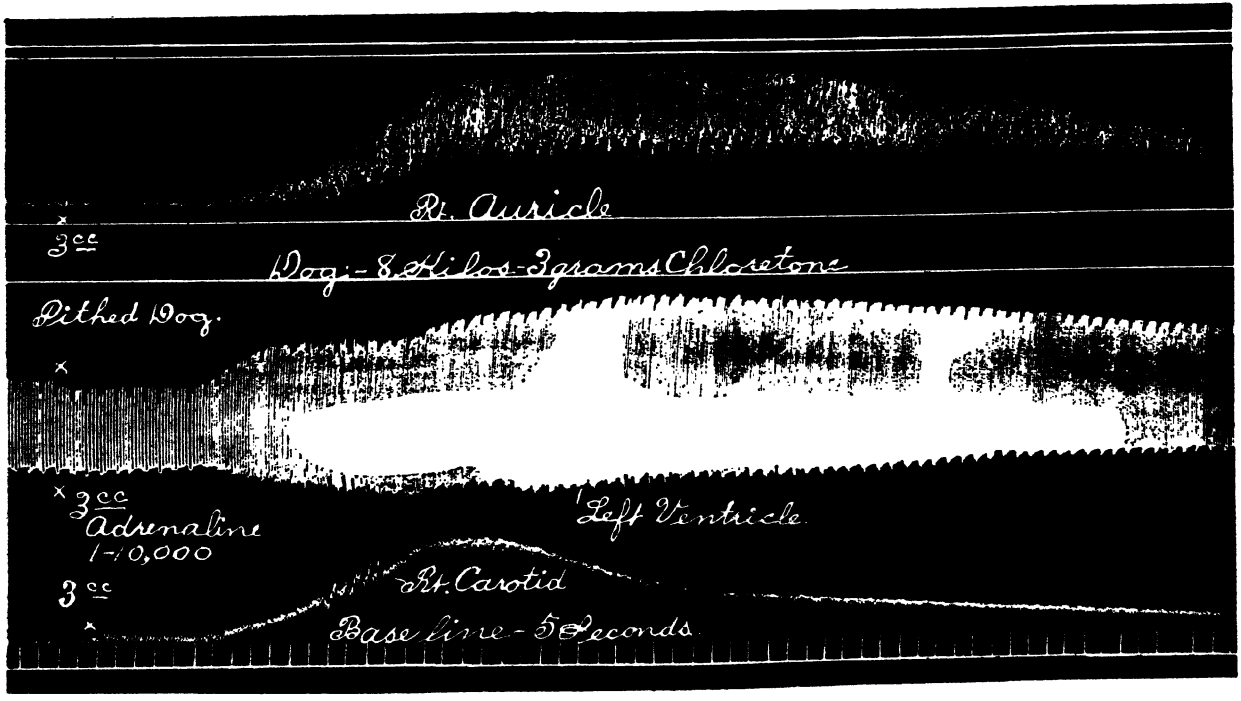


Fig. 13.—Myocardiographic tracings of the right auricle and left ventricle and the blood pressure in a dog. The heart and blood pressure were both greatly depressed at the beginning of the tracing. At the point indicated 3 cc. of adrenalin solution were given intravenously. The action on the auricle, ventricle, and blood pressure is shown very well. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

ACTION ON CIRCULATION.—*Heart.*—Epinephrine acts directly, both on the auricle and ventricle and on the sympathetic cardiac accelerator mechanism (Fig. 13). The heart rate is accelerated, followed by prompt rise in blood pressure. With very rapid rates, cardiac output decreases, and this is followed by fall in blood pressure. The high blood pressure tends to slow the heart due to stimulation of the vagus center (no action if vagus is cut or atropine given intravenously). Cardiac irritability is increased which may eventually lead to ventricular fibrillation.

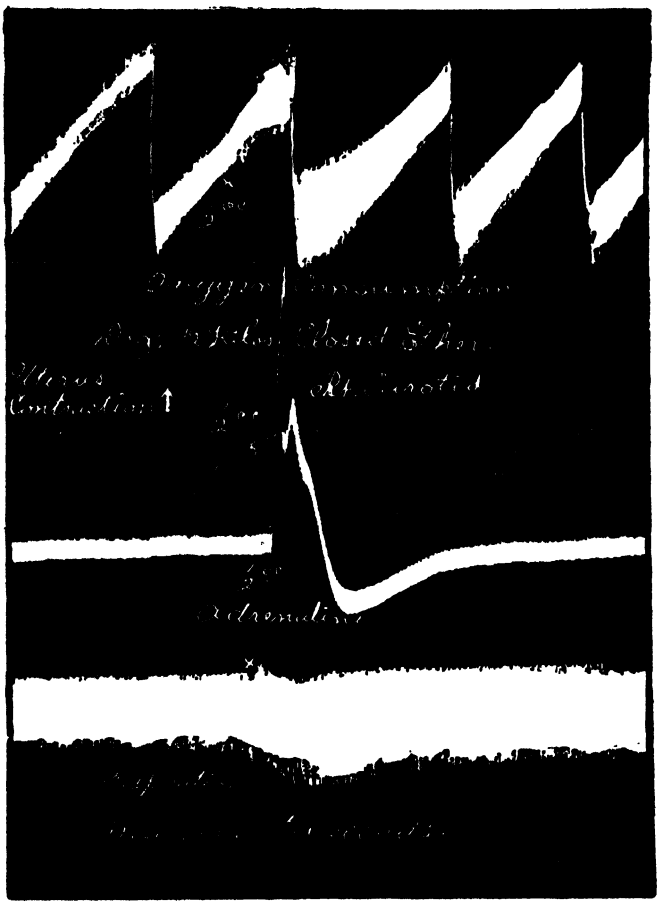


Fig. 14.—Record showing the action of adrenalin on the rate of oxygen consumption, uterine contractions, blood pressure, and respiration. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

Vessels.—The vascular system responds differently to epinephrine. The vessels of the skin constrict (white with anger) and the splanchnic vessels constrict, while the skeletal muscles and apparently the coronary

arteries dilate. The tonic state of activity of the vessels may, however, influence the action of the drug. For example, if the vessels are constricted epinephrine may cause dilatation. This adjustment in body economy is for self-preservation and is explained on the basis of a different degree of development of the sympathetic receptive mechanism.

Epinephrine produces vasoconstriction of all capillaries, except the coronary capillaries, in which it produces vasodilatation. Epinephrine constricts the splanchnic vessels and improves the circulation of striated muscles, thus tending to relieve muscular fatigue.

Blood Pressure.—There is a marked rise in arterial blood pressure due to action on the terminations of the nerves themselves in the smooth muscle, and due to direct action on the muscle of the vessel walls. (Figs. 14 and 15.) The action is on the arterioles chiefly, but also on capillaries and venules (0.005 mg. will show rise in blood pressure). Full therapeutic doses may reach 400 mm. of mercury systolic, and 300 diastolic.

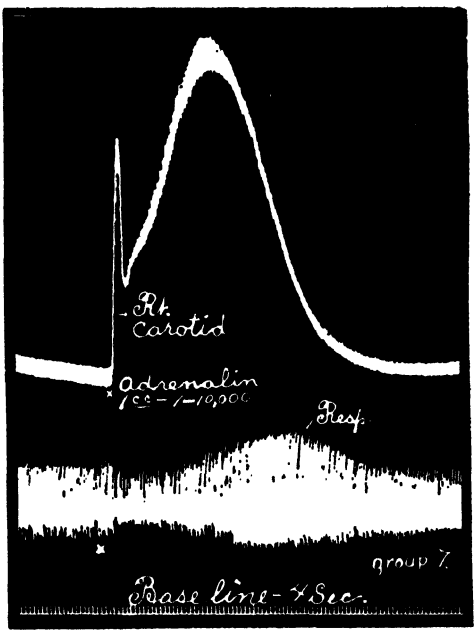


Fig. 15.—Blood pressure and respiration showing the effects of intravenous injection of adrenalin. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

The effect of blood pressure depends on the route of administration: By vein there is a sudden rise of blood pressure which lasts only a short time; by the subcutaneous route, there is a slow rise in blood pressure because epinephrine is slowly absorbed, part is inactivated, and absorption is delayed by local vasoconstriction; orally there is no effect, due to the inactivation of epinephrine by the digestive juices.

ACTION ON GLANDS.—The glandular action of epinephrine is relatively unimportant. The site of action is not on the gland cells but on the sympathetic innervation, presumably on the receptive mechanism.

Salivary Glands.—The salivary secretion becomes thick and rich in organic matter, as after stimulation of the cervical sympathetic. The action does not occur on stimulation of chorda tympani.

Sweat Glands.—The sweat glands provide an exception to the rule, since epinephrine has no effect on the sweat secretions.

Urine.—The urine secretion may be arrested immediately on injection of epinephrine and then increased. This apparently is due to vascular constriction of the renal vessels, followed by early relaxation. The flow of blood through the kidneys, first reduced and then augmented, is due to the dilatation of the renal arteries.

Liver and Spleen.—The liver is affected by the presence of epinephrine, causing *glycogenolysis* with consequent hyperglycemia and glycosuria. The effect occurs with prolonged administration of epinephrine. The accelerated breakdown of glycogen appears to arise from stimulation of the terminal mechanism of the sympathetic nerves of the liver which control glycogenic function. The muscle fibers in the capsules of the spleen contract, and blood corpuscles are thrown into the circulating blood.

The hyperglycemic effect is greatest in well-fed animals with an abundant hepatic store of carbohydrates. If the epinephrine administration be continued, the liver glycogen is converted to glucose which passes into the blood, then subsequently reconverted to glycogen in the muscles (Cori). The cycle is represented as follows:

Muscle Glycogen
↙ ↖
Blood Lactic Acid Blood Glucose
↘ ↗
Liver Glycogen

Action on Stomach and Intestines.—Epinephrine, by vein, causes immediate cessation of stomach and intestinal movements. The splanchnic fibers are inhibitors of these organs, and therefore stimulation of these nerves arrests peristalsis and causes relaxation. The cardiac sphincter reacts in a manner that is dependent on the tonic state of the organ at that time; if the sphincter is relaxed, the drug constricts it and vice versa. The action seems to be on the receptive endings since it occurs after degeneration of the splanchnics. It is not due to paralysis of the vagus (motor nerve to intestine) since stimulation of it shows it to be effective after epinephrine.

Action on Bronchi.—Epinephrine, injected by vein, dilates the bronchi, due to stimulation of sympathetic bronchodilator endings. The relaxation is more pronounced than with atropine.

Action on the Eye.—The action, on intravenous injection, is similar to the action after stimulation of the cervical sympathetic nerve, which causes the pupil to dilate, due to stimulation of the radial nerve fibers. This action also occurs when these fibers are cut. Applied locally to the eye, it constricts the vessels of the conjunctiva and usually dilates the pupil, and reduces the intraocular tension for a short time. There is no cycloplegia, the action being purely mydriatic.

Action on the Uterus, Bladder, and Rectum.—The action on the uterus differs in different animals, and even in the same animal at different times. (Fig. 14.) In the rabbit there is contraction whether the animal is pregnant or not; in the nonpregnant cat, epinephrine generally causes inhibition of movement and relaxation, while in the pregnant cat, the drug is followed by powerful contractions.

Epinephrine lessens the blood supply to the uterus by constricting uterine arterioles. In human beings it lessens the contraction of the pregnant uterus, and may be indicated for the prevention of threatened abortion.

Bladder.—The action depends on the functional state of the organ.

Toxicology.—Occasionally symptoms arise due to overdosage of epinephrine. These symptoms are excitement, anxiety, tremors, precordial pain, and high blood pressure, and although they are quite alarming they subside readily. Such symptoms may occur with therapeutic doses. Patients with asthma may show some degree of hypersensitivity to epinephrine, and more serious major accidents may occur, such as ventricular tachycardia leading to ventricular

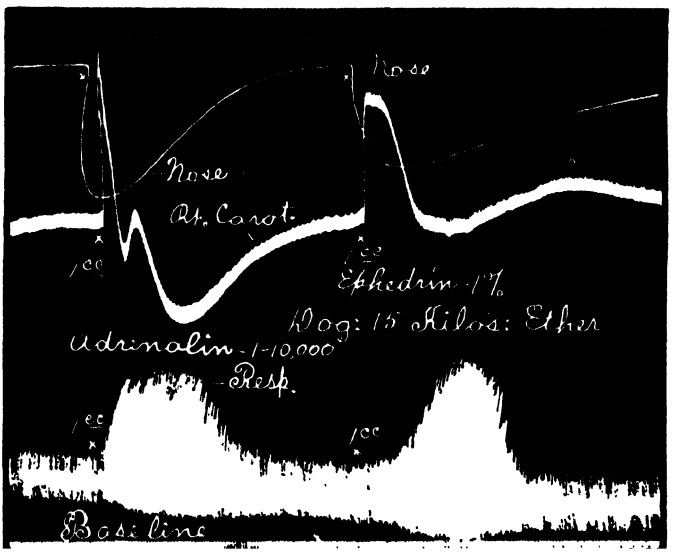


Fig. 16.—A record showing the actions of adrenalin and ephedrine on nasal volume, blood pressure, and respiration. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

fibrillation and death. Such accidents occur from careless employment of the drug and are rare. Extreme care should be exercised in the use of epinephrine for persons suffering from cerebrovascular diseases, angina pectoris, hypertension, etc. The *fatal dose* is unknown, but fatal results have followed injections of 1 cc. of a 1:1,000 solution. The death usually is sudden. The *autopsy findings* are not characteristic. *Treatment* is symptomatic.

Therapeutic Uses.—In medicine epinephrine is used for the following purposes:

1. To stop bleeding from accessible mucous surfaces (epistaxis, hematemesis) or from the skin. *Note:* Due to pressor effect it is of no value in pulmonary hemorrhage, etc.
2. To combat shock.
3. To relax muscles in asthma.

4. To combat certain anaphylactic conditions, e.g., serum sickness.
5. To stimulate respiration and circulation.
6. To enhance action of local anesthetics.
7. To shrink mucous membranes, e.g., membranes of nose, etc.

Epinephrine in solution, or under the trade name of adrenalin (solution 1:1,000), is administered by hypodermic injection. Since some patients show an idiosyncrasy to the drug, it is always best to test out the tolerance of the patient. Great care must be exercised when injecting into a vein. The solution does not keep well and deterioration is fortunately evidenced by a change in color from a clear solution to a brownish solution, usually with a sediment. Ampules containing 1:1,000, 1:500, and 1:100 concentrations are available and are most satisfactory for use.

HEMORRHAGE.—The chief therapeutic use of epinephrine is to constrict blood vessels by local application. A period of secondary dilatation follows such use. In this manner it may be used to diminish hyperemia of conjunctiva, to reduce turbinate swelling, and to reduce hemorrhage of mucosa in surgery of the eye, ear, nose, and throat. It will prevent capillary bleeding. The drug is applied locally only to prevent bleeding. Systemic action does not occur following oral administration, because of destruction in the gastrointestinal tract.

NASAL MUCOSA.—Epinephrine causes a congestion of nasal mucosa, but because of the short duration of its action it has limited value in hay fever or coryza. Oil solutions have longer action. Ephedrine, amphetamine, etc., are to be preferred. (Fig. 16.)

For rhinitis:

℞

Epinephrine Hydrochloride Solution	6.00 cc.	(f℥iss)
Antiseptic Solution	12.00 cc.	(f℥iij)
Water q.s. ad	30.00 cc.	(f℥j)

M. Sig.: Use as spray.

CONJUNCTION WITH LOCAL ANESTHESIA.—Epinephrine is employed with local anesthesia to constrict vessels, thus securing the more efficient and longer action. It has the added value of reducing toxicity of the anesthetic and arresting hemorrhage in the ensuing operation. Since cocaine sensitizes the sympathetic mechanism to epinephrine, very dilute solutions of epinephrine (1:30,000) may suffice.

ALLERGIC CONDITIONS.—Epinephrine (0.3 to 0.5 cc. of 1:1,000) is of great value in giving symptomatic relief in serum reactions, angioneurotic edema, hay fever, urticaria, etc. It is often a life-saver in angioneurotic edema. Its efficient relief of asthma may clinch the diagnosis.

ASTHMA.—*Bronchial Asthma.*—Of all the drugs used in allergy, epinephrine is the most generally useful for all the various allergic crises. It is a life-saver in the control of acute symptoms, often warding off death. Its effectiveness resides in the stimulation of the sympathetic nerve endings which produce results antagonistic to the parasympathetic (vagus) or cholinergic fibers. It thus combats edema and smooth muscle spasm. *Dosage:* 0.2 to 0.3 cc. of the 1:1,000 solution given subcutaneously provides relief in a few minutes in uncomplicated cases. These amounts may be repeated hourly if necessary. Infants and children tolerate such doses. Epinephrine may become less effective after repeated use, at which time aminophylline (0.25 to 0.5 Gm.) should be given intravenously. This often dramatically stops the attack. Administer aminophylline solution very slowly. If necessary, dose may be repeated at twelve-hour intervals.

Cardiac Asthma.—In cases of cardiac asthma, in which bronchial spasm is superimposed on pulmonary congestion, epinephrine (0.3 to 0.5 cc. of 1:1,000 solution) may be given subcutaneously.

NITRITOID REACTIONS.—In the administration of arsphenamine, nitritoid reactions, characterized by flushing of the neck, choking, fall in blood pressure and shock, may occur. This condition may be treated efficiently by epinephrine or ephedrine. An injection of 0.6 cc. of a 1:1,000 solution intramuscularly results in prompt relief. If a shock has already occurred, slowly administer intravenously, 0.2 to 0.3 cc. of epinephrine.

SHOCK.—With our newer conception concerning the cause of shock, epinephrine would seem to be an ideal drug with which to treat the low blood pressure following medical or surgical shock. Shock, however, is attended actually by an increase in capacity of the vascular system and a decrease in the volume of blood, a condition resulting in a fall of blood volume. Epinephrine may fail to produce vasoconstriction because the arterioles are already highly constricted and may even dilate following epinephrine administration.

HEART.—*Heart Block With Syncopal Attacks* (Adams-Stokes Disease).—The subcutaneous injection of epinephrine (0.3 to 0.5 cc. of a 1:1,000 solution) is indicated if syncopal attacks occur. This may increase the heart rate (30 to 50 per minute) for several hours.

Acute Cardiac Failure.—The administration of 0.5 cc. of epinephrine solution following acute cardiac failure resulting from an infectious disease may prove beneficial. The contraindications must be borne in mind. The physician must remember that therapy is directed against a weakened myocardium and no doubt considerable peripheral vasodilatation.

RESUSCITATION.—Epinephrine solution (0.05 to 0.2 cc.) may be given intravenously to initiate heart action following anesthetic accidents, drowning, etc. If the pulse is not palpable and heart sounds are not audible, an injection of 0.5 cc. may be advisable as a last resort. Since there is always the danger of initiating ventricular fibrillation from this procedure, other measures are indicated, such as cardiac massage and artificial respiration.

ADDISON'S DISEASE.—Epinephrine is used orally, or by injection, to supply deficiencies in Addison's disease. Solution of Epinephrine Hydrochloride, U.S.P. (10 minims of the 1:1,000 solution three times daily), or extract of the suprarenal gland, may be given, but the benefit is usually temporary.

HYPOGLYCEMIA.—Hypoglycemia in diabetes mellitus may be treated by injection of 1 cc. of solution of epinephrine. If ineffective, do not repeat.

Epinephrine is effective in combating the *insulin reaction;* however, there is little reason to use the drug if carbohydrates are at hand. The dose is 1 cc. of the 1:1,000 solution for adults, and 0.5 cc. for a child, given intramuscularly.

Bio-Assay.—*Chemical.*—Oxidation leads to various colored compounds. This action is not specific for epinephrine.

Biological.—The official method of assay is based upon the rise of blood pressure in the anesthetized dog. A U.S.P. reference standard is available.

PREPARATIONS

Epinephrine, *Epinephrina,* U.S.P. *Adrenalina,* B.P. *Dosage:* Hypodermic 0.5 mg. (1/120 grain).

Epinephrine Solution, *Liquor Epinephrinae,* U.S.P. A solution of epinephrine hydrochloride in distilled water with a potency equivalent to a solution containing 1 Gm. of U.S.P. Epinephrine Reference standard in each 1,000 cc. *Dosage:* By parenteral injection 0.5 cc. (8 minims).

Epinephrine Hydrochloride Inhalation, *Inhalatio Epinephrinae Hydrochloridi,* U.S.P. Solution of epinephrine hydrochloride in distilled water.

Epinephrine Injection, *Injectio Epinephrinae,* U.S.P. A sterile solution of epinephrine hydrochloride in water for injection. The usual sizes contain 1 cc., 10 cc., and 30 cc. of 1:1,000 solution.

Ephedrine

Ephedrine (alpha-hydroxy beta-methyl-amino-propylbenzene) is a vegetable alkaloid isolated in 1887 by Nagai from the Chinese herb ma huang ("yellow astringent"), botanically known as *Ephedra vulgaris,* var. *helvetica,* a plant which resembles the yew tree and has a pleasant aromatic odor. This alkaloid, which has been used as a medicine by the Chinese since antiquity, was introduced into therapeutics in the Western hemisphere by K. K. Chen in 1926.

The main supply of the drug is still from natural sources, although the synthetic product is available. The drug is an almost colorless solid occurring as crystals or granules which are soluble in water or alcohol.

Pharmacological Action.—Ephedrine excites the nervous system, producing effects resembling those of epinephrine. Ephedrine augments the effects of injected epinephrine or sympathetic stimulation. Its action is probably due to an inhibition of the destruction of sympathin by amine oxidase.

It differs from epinephrine in that ephedrine can be absorbed from the intestinal tract and thus can be used orally. After oral administration the nasal mucosa can even be shrunk. Ephedrine has a more prolonged action on the cardiovascular system, the action being slower in onset and weaker in action. Regardless of the dose or prior administration of other drugs there is no vasodilatation with ephedrine as is occasionally found with epinephrine. The rise in blood pressure following administration of epinephrine is proportional to the dose, while with ephedrine large doses may cause a fall in blood pressure. This fall in blood pressure is attributed to the more direct action of ephedrine on the heart, therefore ephedrine may produce its rise in blood pressure by this mechanism rather than by peripheral vasoconstriction. Ephedrine is of little use with local anesthetics.

Ephedrine is a valuable respiratory stimulant acting directly on the respiratory center, while epinephrine is valueless for this purpose. Ephedrine is useful in ophthalmic work due to its dilating action on the pupil, an action resulting from either local or systemic administration. Epinephrine also has a mydriatic action.

Small doses of ephedrine stimulate the cerebrum. It has been used to antagonize the effect of barbiturates, morphine, and chloral in narcotized animals.

Toxicology.—Toxic doses of ephedrine stimulate the nervous system and depress the heart. In man doses below 0.10 gram rarely cause symptoms of perspiration, tremor, palpitation and faintness; they are sometimes present after larger doses. *Treat* by administering hot applications to relieve peripheral arterial constriction, and sedatives, such as barbiturates, for excitement and delirium. The use of the drug should be avoided in hyperthyroidism, cardiac diseases, and nervous patients.

Therapeutic Uses.—Ephedrine is employed in oily and aqueous solutions, alone or with other agents, in sprays, instillations, etc. Probably the greatest danger lies in self-medication.

Bronchial Asthma.—Ephedrine is of great value in preventing or aborting attacks of asthma. The drug may readily give relief in mild cases. The average dose recommended is from 25 to 50 mg. of ephedrine sulfate, administered several times per day.

Ephedrine has been shown by many to be very reliable in relieving and preventing attacks of asthma. When given orally it takes ten to thirty minutes to act, and the action lasts for several hours. In severe and even moderate cases it may not be effective, while epinephrine is very dependable.

Hay Fever, Rhinitis, Sinusitis.—The congested nasal mucosa may be relieved by use of an ephedrine spray, ointment, or jelly. Some hay fever sufferers may be completely relieved from symptoms of hay fever. Ephedrine is usually given orally, but a nasal spray may add to the patient's comfort. The action is rapid, following local application, and may last two or three hours. The rationale of such treatment may be questioned, but it affords great relief by opening the nasal airway and relieving nasal congestion. One per cent ephedrine base in oil, several unofficial ointments, glycerites and inhalant preparations, are available for use on mucous membranes (N.N.R.).

Ephedrine is also effective by mouth, for which use a convenient prescription for allergic rhinitis (hay fever) is the following:

℞

Ephedrine Sulfate	0.025 (gr. ⅜)
Phenobarbital	0.050 (gr. ¾)
Aminophylline	0.200 (gr. iij)

M. and make 24 such capsules.
Sig.: 1 capsule 3 times a day.

Aside from asthma and hay fever, good results have been reported in *serum sickness, urticaria, angioneurotic edema,* and *nitritoid reactions.* In the treatment of nitritoid reactions ephedrine sulfate may be administered, several doses orally of 0.025 gram (⅜ grain) each on the day before and the day of ingestion of neoarsphenamine.

For hay fever, etc:

℞

Ephedrine Sulfate	1.00 Gm. (gr. xv)
Calcium Lactate	4.00 Gm. (ʒj)

Pone in capsulas No. xxx.

Sig.: One capsule three or four times daily.

For nasal spray in hay fever:

℞

Ephedrine Sulfate	0.30 Gm. (gr. v)
Solution of Physiological Sodium Chloride	30.00 cc. (fʒj)

M. Sig.: Use as spray.

Circulatory Depression.—Ephedrine is recommended for treatment of shock and hemorrhage, and other conditions associated with low blood pressure. In serious circulatory collapse it is probably useless.

Hypotension.—In *chronic* hypotension ephedrine makes the patient feel much better. In *postural* hypotension, resulting from lack of normal reflex, cardio-accelerator and vasoconstrictor responses, striking

results are obtained. The dose recommended is 25 to 50 mg. orally every three hours during activity. The beneficial action is thought to be due to central action on the brain. The usual dose is 60 to 90 mg. (1 to 1½ grains) by mouth. In doses of 50 to 100 mg., given orally or subcutaneously, ephedrine sulfate raises the blood pressure and increases the pulse rate for a period of several hours.

For hypotension:

℞

Ephedrine Sulfate ---------- 0.50 Gm. (gr. viiss)
Pone in capsulas No. xv.

Sig.: One capsule every three hours.

Complete Heart Block With Syncopal Seizures (Adams-Stokes Disease).—Ephedrine may be given orally in doses of 20 to 30 mg. three times daily. If smaller doses will suffice, smaller doses should be administered. The drug is contraindicated when periodic ventricular fibrillation is the cause.

Narcolepsy.—Ephedrine is an excellent drug in the treatment of this condition. The rationale for its use is not thoroughly understood, but we know it gives symptomatic relief, probably through its action on the central nervous system. A dose of 10 to 50 mg. of ephedrine sulfate is given orally three times daily. Children tolerate the drug well. Ephedrine is not a cure, but affords considerable symptomatic relief, an action not shared by epinephrine.

Myasthenia Gravis.—Ephedrine produces beneficial results in the treatment of this disease a few hours after administration. An oral dose of 10 to 25 mg. two or three times daily is recommended. Many patients are restored to fairly normal existence. Ephedrine and glycine therapy may be combined. Here again epinephrine has no therapeutic value.

Mydriatic.—A 1 to 3 per cent solution of ephedrine sulfate is recommended as a useful mydriatic for routine ophthalmic examination. It causes satisfactory pupil dilation in thirty minutes or more, which lasts several hours. There is no paralysis of accommodation and no increase of intraocular pressure. Ephedrine solutions combined with 0.1 per cent homatropine give excellent mydriasis without cycloplegia.

Spinal Anesthesia.—In spinal anesthesia ephedrine is the drug of choice. Twenty-five to 50 mg. of ephedrine sulfate are given subcutaneously, prior to the use of procaine. With the use of ephedrine in spinal anesthesia cases of hypotension or hypertension are not contraindicated. If, however, ephedrine fails, use epinephrine.

Antidote.—Ephedrine is an excellent antidote against depressant drugs, such as morphine, barbiturates, etc. Doses of 50 mg., by stomach tube or subcutaneously, repeated if necessary, are indicated. An intramuscular injection of 20 to 30 mg. may be indicated. The drug raises the blood pressure and acts as a powerful respiratory stimulant.

Preparations

Ephedrine, *Ephedrina,* U.S.P.

Ephedrine Hydrochloride, *Ephedrinae Hydrochloridum,* U.S.P. *Dosage:* 0.025 Gm. (⅜ grain). B.P., 0.016-0.1 Gm. (¼-1½ grains).

Ephedrine Sulfate, *Ephedrinae Sulfas,* U.S.P. *Dosage:* 0.025 Gm. (⅜ grain).

Ephedrine Sulfate Tablets, *Tabellae Ephedrinae Sulfatis,* U.S.P. The usual sizes contain 15 mg., 25 mg., and 30 mg.

Many preparations are available in N.N.R. and N.F.

SYNTHETIC SYMPATHOMIMETIC DRUGS

A vast number of synthetic sympathomimetic drugs have been prepared and tested clinically. They have been prepared to eliminate the undesirable side effects of epinephrine and ephedrine. Many of them vary greatly from the sympathomimetic patterns of epinephrine or ephedrine and must be evaluated on their ability to measure up to the clinical uses for which they are recommended. Among the newer drugs the following are of special interest:

Amphetamine (Benzedrine)

Amphetamine is a synthetic racemic desoxy-nov-ephedrine ($C_6H_5CH_2$-$CHNH_2CH_3$) structurally related to both ephedrine and epinephrine, and possessing the fundamental grouping responsible for vasoconstrictive properties. It is a volatile liquid; the carbonate which is also volatile is used for its volatility and its vasoconstrictor action in inhaler tubes. The unpleasant odor is masked by menthol and oil of lavender. The average dose obtained from inhalation would be far from the dose required to produce toxic symptoms.

Pharmacological Action.—Amphetamine is a sympathomimetic drug which stimulates the higher centers, especially the cortex. It is a vasoconstrictor with a potency greater than that of ephedrine. Administration of amphetamine, either orally or subcutaneously, increases the blood pressure, depresses respiration slightly (Fig. 17), and also raises the spinal fluid pressure. The red cell count increases following the administration of amphetamine for several days. The drug stimulates the central nervous system, relieving the feeling of fatigue and depression; the effect lasts from two to five hours. Its use has achieved established recognition in the treatment of narcolepsy, for pathological drowsiness and catalepsy. The gastrointestinal tract shows decreased tone and motility following the use of this drug.

Workers report few reactions following amphetamine administration. Delirium and extreme motor activity have resulted from large doses of amphetamine. Habit formation may occur.

Therapeutic Uses.—*Asthma, Hay Fever, Sinusitis, etc.*—Amphetamine may be used orally, or applied locally, for the treatment of all congestive processes of the upper respiratory tract, such as colds, sinusitis, vasomotor rhinitis, and hay fever. Benzedrine sulfate is indicated for oral use, and an oil spray is recommended for local application.

Gastrointestinal Spasm: X-ray Diagnosis of Stomach.—Amphetamine stimulates the receptive mechanism of the gastrointestinal tract and thus induces relaxation of spasm. This ability to relax reflex and functional pyloric spasm has made it an important diagnostic aid in x-ray work. It decreases the emptying time of the stomach and allows for better filling and visualization of the duodenum and bulb; the average dose is 10 to 30 mg., depending on the result to be obtained. The proper action is secured in from fifteen to thirty minutes after oral administration.

Its therapeutic application in spastic colitis and spastic constipation has been suggested.

Mild Depressive Neuroses.—While amphetamine is probably without effect in the major mental disorders, Myerson (1936) has stated that: "In certain cases of the neuroses associated with depression, fatigue

and anhedonia, and in certain cases of the minor stages of the psychoses of the same general type benzedrine sulfate acts as an ameliorative influence."

Hypotension.—A dose of 25 mg. taken before arising and doses of 5 to 15 mg. at intervals during the day are indicated for the treatment of orthostatic hypotension.

Narcolepsy.—Benzedrine sulfate, orally, in doses of 10 mg. two or three times a day, has proved effective in controlling narcoleptic and cataleptic seizures, but sometimes a larger dose is necessary. Benzedrine is apparently more efficient than ephedrine, as it possesses a low toxicity, and its actions are prolonged.

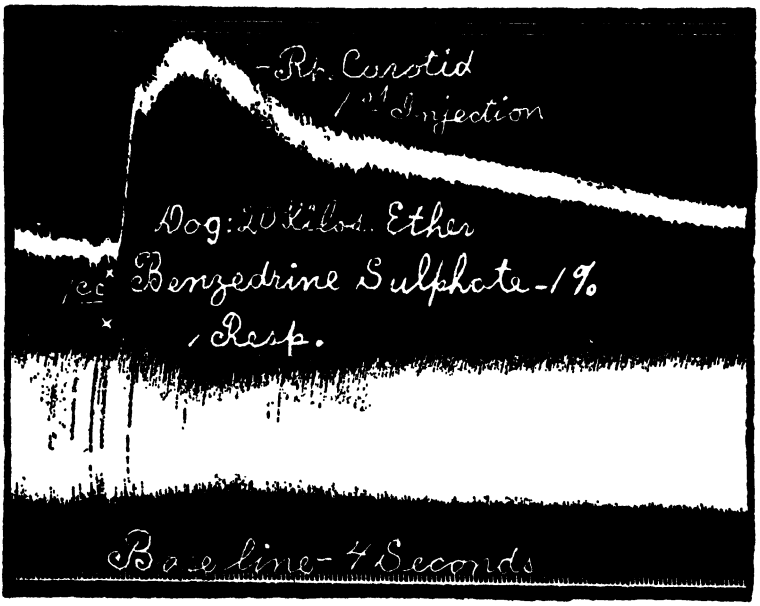


Fig. 17.—Effect of amphetamine (benzedrine) on blood pressure and respiration. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

Evidence seems to indicate that amphetamine sulfate is useful in the treatment of *migraine.* It may be used as a substitute for ergotamine tartrate when the latter is either ineffective or productive of severe toxic symptoms. It may be administered orally daily in small amounts as a means of preventing attacks.

Obesity.—Amphetamine, 10 mg. daily in the morning, has been used to facilitate weight loss, presumably by producing anorexia. Danger of habituation is to be borne in mind. Results are seldom good except in patients who simultaneously follow a reducing diet.

Parkinsonism.—A combination of a drug of the belladonna group with amphetamine, 10 to 30 mg. twice daily, is suggested as an adjunct in the treatment of this condition.

Miscellaneous.—Benzedrine sulfate is a useful adjunct in the treatment of chronic *alcoholism.* Bloomberg (1939) recommends 20 mg.

daily, one-half of the dose on rising and the other half at noon, but this must be adjusted to meet the requirements of the individual patient. In *alcoholic psychoses* the normal dosage used by Davidoff and Reifenstein (1938) in institutionalized patients was 20 to 30 mg. orally or intravenously. Benzedrine has proved of some value in certain mental diseases; for example, in *chronic nervous exhaustion,* impaired mental efficiency, lowered mood and apathy, fatigue, etc., excellent results have been obtained in some cases. Normally benzedrine (10 to 20 mg.) produces a condition of lessened fatigue, talkativeness, and general feeling of well-being. The object of the treatment is to stimulate these qualities in the patient not possessing them. *Its potentially harmful effects, such as habit-formation and cardiac overstimulation, raising of blood pressure, and mental and physical overstimulation, must be borne in mind.*

PREPARATION

Amphetamine Sulfate, N.N.R. (Benzedrine). Sympathomimetic and central stimulant. *Dosage:* 5 to 10 mg. ($\frac{1}{12}$ to $\frac{1}{6}$ grain) orally; inhalation of volatile salt in nasal inhalator.

Phenylephrine (Neosynephrine)

Phenylephrine hydrochloride is a synthetic, optically active sympathomimetic amine which has replaced an older preparation *synephrin.* Phenylephrine hydrochloride is laevo-α-hydroxy-β-methylamino-3-hydroxy ethylbenzene hydrochloride ($C_6H_4OH.CHOHCH_2NHCH_3.HCl$).

Action and Uses.—The pharmacological actions of phenylephrine are similar to those of epinephrine. The effect on the heart is less than that of epinephrine, compensatory reflexes may slow the heart to below normal. The incidence of side reactions is less than with epinephrine. Finally, phenylephrine is much more stable and produces more lasting responses than does epinephrine.

Phenylephrine is extensively used topically on nasal mucous membranes for symptomatic relief of vasomotor rhinitis and sinusitis. It is employed for topical application as a 0.25 to 1.0 per cent solution in 0.8 per cent sodium chloride and 0.1 per cent sodium benzoate. It is also a suitable agent for sustaining blood pressure during spinal anesthesia, being superior to ephedrine in that it does not affect the central nervous system, and does not lose its efficacy with repeated use. For this purpose inject 5 mg. in physiological saline subcutaneously, repeat if necessary.

As an adjuvant to local anesthetics, three to four drops of a 1 per cent solution of phenylephrine to 10 cc. of 2 per cent procaine give excellent results. This solution may be boiled.

PREPARATION

Phenylephrine Hydrochloride, N.N.R. *Dosage:* See N.N.R.

Kephrine

Kephrine closely resembles epinephrine pharmacologically, but its actions are less potent and more persistent, and its solutions are more stable. Local effects require about ten times, and systemic pressor action sixty times, the dosage of epinephrine. It is used chiefly as a local hemostatic. The vasoconstriction lasts over an hour. It is

inactive by mouth. Kephrine is injected hypodermically for asthma (2 cc. of 0.5 per cent solution). It has no special advantage over epinephrine.

Paredrine

Paredrine is a sympathomimetic amine. It is more stable than epinephrine and is quite free from actions on the central nervous system. It shows promise of being a valuable mydriatic agent and also a vasopressor agent. Its actions on the bronchi and gastrointestinal tract are not sufficiently great to be of clinical use.

As a *mydriatic agent* it is useful. A 1 per cent solution produces complete dilatation of the pupil within forty-five minutes and the effect lasts two hours. There is little action on accommodation and no significant change in intra-ocular pressure. Paredrine is an active *pressor agent* during spinal anesthesia. Good pressor affect may be obtained with 10 or 20 mg. intramuscularly, 5 to 10 mg. intravenously, or both. Toxic reactions are rare.

Propadrine Hydrochloride

Propadrine hydrochloride is the monohydrochloride of a base resembling ephedrine (laevo-α-hydroxy-β-methyl-amino-propyl-benzene hydrochloride) but differs in that the methyl group on the amino group is replaced by a hydrogen atom.

Action and Uses.—Propadrine hydrochloride acts similarly to ephedrine. A 1 per cent aqueous solution or 0.66 per cent jelly is recommended to produce constriction of capillaries and shrinking of swollen mucous membranes. It is claimed that its action is somewhat more prolonged than that of ephedrine and that the anxiety complex, so common with the use of ephedrine, is less apparent.

The drug may also be administered orally, three-eighths grain capsule every two to four hours, as indicated. Although no toxic manifestations are on record, continued overdosage should be avoided as with other similar drugs of this group.

Preparation

Propadrine Hydrochloride, N.N.R. *Dosage:* See N.N.R.

Naphazoline (Privine)

Naphazoline hydrochloride is a vasoconstrictor, which, when applied to nasal mucous membranes, causes a prolonged reduction of local swelling and congestion. The site of action is probably the peripheral sympathetic nerve endings. No information is available in regards to its effect on blood pressure following local application.

It is recommended for symptomatic relief of disorders of the upper respiratory tract such as rhinitis, rhinosinusitis, and nasal congestions of allergic and inflammatory origin.

Dosage: Several drops of 0.05 to 0.1 per cent solution for adults. For children use 0.05 per cent solution.

Preparation

Naphazoline Hydrochloride, N.N.R.

Tuamine

Tuamine, N.N.R., produces effective vasoconstrictive action upon inhalation of the vapors. This procedure provides an effective method of treatment of acute rhinologic conditions and has added usefulness

when prolonged medication is indicated. It should be used with caution in persons who have cardiovascular disease. It is available in an inhaler devise.

Tuamine sulfate in a 0.5 per cent solution produces a vasoconstrictive action equivalent to a similar concentration of epinephrine. The duration of the effect is longer than ephedrine. A 1 per cent solution may be applied to mucous membranes. A 2 per cent solution may be used on operative procedures.

Vonedrine

Vonedrine, N.N.R., base is volatile and therefore effective by inhalation, serving as a nasal vasoconstrictor. It is reported to produce little irritation, tissue reactions, or central nervous system and cardiovascular stimulation. It is available in an inhaler.

Tyramine

Tyramine, para-hydroxyphenylethylamine, is closely related to epinephrine in structure and produces very similar sympathomimetic stimulation. Tyramine may be produced from the amino-acid tyrosine by the removal of the carboxyl group. This may occur in the presence of putrefactive organisms. Tyramine also occurs in ergot preparations. The drug was first identified in putrefying flesh.

$$\underset{\text{Tyrosine}}{C_6H_4OHCH_2CH(COOH)NH_2} = \underset{\text{Tyramine}}{C_6H_4OHCH_2CH_2NH_2} + CO_2$$

Action and Uses.—The action of tyramine is similar to that of epinephrine, but its action is weaker and more prolonged, probably due to an action on the muscle also. Tyramine does not, however, appear to exert the characteristic local vasoconstrictor effect on mucous membranes when applied locally as does epinephrine. Intravenous injections produce a rise in blood pressure lasting two to three minutes. It is fairly effective in arresting superficial hemorrhage. It is not reliable as a substitute for ergot in labor or postpartum hemorrhage. It has been suggested as a therapeutic agent to raise the blood pressure in collapse, to stimulate the uterus during labor, and to guard against respiratory depression by morphine.

SYMPATHOLYTIC DRUGS

The sympatholytic or orthosympatholytic drugs are agents whose effects on the body resemble the effects of cutting the sympathetic nerve supply to various organs. Such drugs, generally, would be antagonistic to epinephrine, would slow the heart, lower blood pressure by vasodilation, increase gastrointestinal muscle tone, etc., by antagonizing the sympathetic nervous mechanisms.

Several drugs, such as ergotoxine, ergotamine, yohimbine, and certain dioxane derivatives, imidazoline derivatives, and dibenzamine hydrochloride, have depressant action on the sympathetic nervous system. Unfortunately, they are too toxic for routine clinical use.

Ergotoxine and Ergotamine

Ergotoxine ($C_{32}H_{41}N_5O_6$) and *ergotamine* ($C_{33}H_{35}N_5O_5$) are alcohol-soluble alkaloids found in ergot. *Ergotoxine*, an amorphous alkaloid, is rather unstable and by loss of water changes to the crystalline alkaloid

ergotinine, $C_{35}H_{39}N_5O_5$. *Ergotamine,* a crystalline alkaloid, is the levorotatory isomer of ergotaminine which is also crystalline, but less active than ergotamine.

Pharmacological Action.—*Sympathetic Nervous System.*—These drugs are sympathetic nervous depressants. They inhibit the action of epinephrine on the tissues in a selective manner. Ergotoxine depresses only the augmentor functions of the peripheral sympathetic mechanism, while ergotamine paralyzes both the augmentor and inhibitor functions.

A therapeutic dose of ergotamine (0.5 mg.), administered subcutaneously, produces no reversal of the epinephrine rise in blood pressure, but produces a slight inhibition in the elevation of the metabolic rate and in the production of blood sugar, as produced by epinephrine.

Smooth Muscle.—Both drugs produce complex stimulant effects on smooth muscle, and are particularly active in producing uterine contraction and contraction of arterioles. The stimulant action on the smooth muscle of arterioles produces a rise in blood pressure. The stimulant action on the puerperal uterus occurs only when these drugs are given by intramuscular injection and in optimal dose (0.5 mg.). The response appears in fifteen to forty-five minutes and is of varying intensity. The uterine effects are unreliable following oral administration, while ergot preparations are quite reliable when given by mouth.

Action in Migraine.—The mode of action in migraine is in doubt. It may act directly on smooth muscle of the arterioles, or by paralysis of the cells, or by some other method or combination of methods. The dose effective in migraine would hardly be sufficient to paralyze sympathetic nerve endings, and there is a question whether constriction of blood vessels will relieve headache.

Toxicology.—Since these drugs have a marked cumulative action, they must be used with caution. Cases of gangrene have followed the administration of 10 mg., which is about twice the therapeutic dose. Common toxic symptoms are nausea and vomiting which may follow the administration of the drugs. Atropine sulfate (0.5 mg.) by injection is the antidote. Other symptoms are muscle pains, throat constriction, and numbness and tingling of the fingers and toes. Muscle pains may be relieved by the intravenous administration of calcium gluconate. Cardiac and peripheral vascular diseases contraindicate the use of ergotamine.

Therapeutic Uses.—*Migraine Headache.*—Ergotamine tartrate is indicated for the treatment of migraine headache. *Dosage:* 0.25 mg. or $\frac{1}{250}$ grain subcutaneously, to be followed in 2 or 3 hours by 0.5 mg. or $\frac{1}{125}$ grain. The oral dose of 1 mg. or $\frac{1}{60}$ grain in tablet form is not so effective as the subcutaneous dose of the drug. Parenteral injections are effective in approximately 90 per cent of cases and oral administration in from 40 to 70 per cent. The frequency of the headaches is not affected, nor is a cure effected. The drug is more effective if given early in the attack. Relief occurs in from fifteen minutes to two hours. No tolerance to the drug is shown.

As Oxytocic.—Ergotamine, like ergotoxine, when given by intramuscular injection and in an optimal dose of at least 0.5 mg. produces the desired effect in accelerating delivery. Ergotamine tartrate is also indicated in hemorrhage following abortion, after curettage, and in postpartum endometritis.

Shock.—Ergotoxine ethanesulfonate has practically the same pharmacological actions as ergotamine tartrate. The intramuscular injection of $\frac{1}{120}$ to $\frac{1}{60}$ gr. is indicated in *shock* and also as an antidote for scorpion toxin.

PREPARATIONS

Ergotamine Tartrate, *Ergotaminae Tartras,* U.S.P. *Dosage:* 0.5 mg. (1/120 grain).

Ergotamine Tartrate Tablets, *Tabellae Ergotaminae Tartratis,* U.S.P. Usual sizes contain 0.5 mg. and 1 mg.

Yohimbine

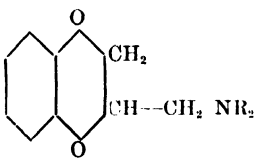
Yohimbine is an alkaloid isolated from the bark of the Yohimbe tree. It possesses local anesthetic action like cocaine but is more lasting. Mydriasis occurs without loss of accommodation. The systemic effects vary with the dose and mode of administration. Large doses intravenously *reverse epinephrine* and dilate the renal vessels. It does not interfere with the pressor response to electric sympathetic stimulation, or of nicotine or acetylcholine in atropinized animals. It diminishes other epinephrine effects (Hutchinson, 1942).

When given by mouth or hypodermically in moderate doses, it produces general vasodilation in the skin, mucous membranes, and particularly the sexual organs. In consequence of the latter, and perhaps by a direct action on spinal centers, it produces erection. It does not seem to stimulate the production of spermatozoa or sexual desire. The reports of clinical improvement by its use are probably explainable by suggestion. The therapeutic dose for man is given as 5 mg. or 1/12 grain.

Toxicology.—Large doses produce psychic excitement, cerebral congestion, vertigo, and gastric disturbance. Toxic doses produce general stimulation and, later, paralysis of the nervous centers with death, finally, by respiratory paralysis.

Dioxane Derivatives

E. Fourneau has synthesized a series of dioxanes of the general formula



Among the most extensively studied are:

F 933 (piperidomethyl-3-benzodioxane). This substance appears to be adrenolytic but not sympathetic. It is of little clinical value due to side reactions.

F 883 (diethylaminomethyl-3-benzodioxane) is thought to be both adrenolytic and sympathetic. Due to side reactions it has little value clinically.

Recent studies on dibenzyl-b-chlorethylamine (dibenzamine hydrochloride) and its derivatives indicate that some members of this group may prove to be clinically useful adrenolytic and sympatholytic agents.

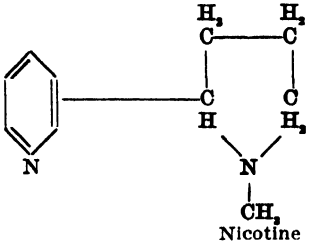
The sympatholytic properties of numerous imidazoline derivatives have been studied. Two of these 2-benzyl-4, 5imidazoline (priscol) and N,N-dibenzyl-β-chlorethylamine (dibenzamine) are reported to give promising clinical results.

DRUGS ACTING ON THE SYMPATHETIC GANGLIA AND PARASYMPATHETIC GANGLIA

Drugs which act on the sympathetic and parasympathetic ganglia include nicotine, lobeline, coniine and gelsemine. Tetraethylammonium chloride blocks transmission of nervous impulses across autonomic ganglia.

Nicotine Group

Nicotine, $C_{10}H_{14}N_2$, the chief alkaloid of tobacco *(Nicotiana tabacum)*, occurs in tobacco leaves in amounts from 1 to 7 per cent. The alkaloid is a colorless and almost odorless liquid, which turns brown and acquires the characteristic odor of tobacco on exposure to air. It is soluble in water, alcohol, and ether. Nicotine has no therapeutic value, but is of interest toxicologically because of the large quantities of tobacco used in the United States.



Nicotine

Pharmacological Action.—The chief actions of nicotine are light stimulation, followed by paralysis of (1) autonomic ganglia (sympathetic and parasympathetic), and (2) the central nervous system. This drug has a characteristic curare action on skeletal muscle.

Nicotine is readily *absorbed* from the oral and gastrointestinal mucosa and from the respiratory tract. Sufficient absorption may take place from the skin to produce severe poisoning. The drug is *detoxified* mainly by the liver, and the remainder is excreted, chiefly in the urine. Excretion is fairly slow; it requires three to four days for the drug to disappear from urine after the individual has ceased smoking.

Action on Ganglia.—Nicotine first stimulates, then paralyzes, all autonomic ganglia. It has no action on the posterior root ganglia and, no doubt, no action on any other sensory ganglion. For example, if nicotine is painted upon a spinal root ganglion (in which are situated nerve cells but no synapses) it does not affect conduction along the posterior root fibers.

According to Langley the paralytic effects of nicotine are exerted on the ganglia, for the action of the postganglionic fibers remains effective.

Action on Central Nervous System.—There is stimulation, followed by depression, of the entire cerebrospinal axis. The stimulative effect may be absent in large doses. The *spinal cord* is thrown in a condition of exaggerated irritability by stimulation of the motor cells, which often results in convulsions. The convulsions seem to be due to action on the medulla oblongata and hindbrain, as the convulsions are of a clonic type, and are much weaker after division of the cord just below the medulla than in the intact animal. *Medullary* stimulation is indicated by a slow heart rate and deepened respiration. *Respiration* is first increased, and then depressed, chiefly through the cardio-aortic

and sino-carotid reflex. Large doses cause depression and paralysis of the respiratory center. Salivation and vomiting, according to Eggleston and Hatcher, are probably due to medullary stimulation, but may be, in part, due to the powerful contractions of the stomach and intestinal walls. Large doses may cause obliteration of the lumen. The action is stopped by atropine which paralyzes the postganglionic terminations.

Action on Circulation.—After moderate doses the *heart* becomes slow and may stand still in diastole for a few seconds; it then resumes its former action, possibly slightly accelerated, due to paralysis of the ganglia. The slow pulse is due to stimulation of the vagus ganglia. This action is prevented by atropine, which paralyzes the terminations of the postganglionic fibers, and thus blocks the passage of impulses from the ganglia to the muscle. The action is also prevented by curare and coniine which paralyze the ganglia.

The period of stimulation of the ganglia is short and is soon followed by paralysis, so that on stimulating the vagus, after nicotine, there is no slowing of the heart, but acceleration, because the accelerating fibers have no ganglia in the heart muscle and are therefore unaffected by nicotine.

There is usually an increase in *blood pressure* due to peripheral vasoconstriction (Pilcher and Sollmann), and due also to stimulation of the ganglia (Hoskins and Ransom). There may be a secondary fall of pressure due to paralysis of the ganglia (Lee, 1908).

The *coronary vessels* are constricted, producing a decreased coronary circulation, notwithstanding the raised blood pressure. The renal and pulmonary vessels are constricted.

Greene summarizes the action of nicotine on circulation in Table XVII.

TABLE XVII

ACTION ON:	DOSE		
	WEAK	MEDIUM	TOXIC
Blood pressure	Rise	Rise	Fall
Heart rate	Slow	Rapid	Slow and falling
Heart amplitude	Increased	Greater	Less
Vagus control	Strongly increased	Decreased and lost	
Accelerator control	Increased	Increased	Decreased and lost
Vasomotors	Increased	Decreased	Lost

Action on Pupil.—In man, nicotine poisoning causes contraction of the pupil, followed by dilatation. This effect on the eye is due to its action on the autonomic ganglion, and the result will be the sum of its effects on the ciliary (parasympathetic) and the cervical (sympathetic) ganglia, which are usually first stimulated and later paralyzed.

Action on Smooth Muscle.—Nicotine causes pronounced stimulation of *the gastrointestinal tract,* resulting in repeated evacuations. Large doses may obliterate the lumen. This action seems to be on the Auerbach plexus, as it is abolished by section of all nerves and also by atropine which paralyzes the postganglionic terminations.

Action on Secretions.—The secretions of glands are increased temporarily by nicotine, then depressed. Large doses diminish the activity immediately. The site of action is the ganglia of the secretory nerves.

Pilocarpine and muscarine cause profuse salivation after nicotine because they stimulate the postganglionic terminations in the gland cells; a central connection is immaterial.

Curare Action on Skeletal Muscle.—Nicotine has a curare effect, especially in large doses. Small doses cause fibrillary twitching in muscles in which the nerve ends have degenerated from section.

Toxicology.—Numerous cases of poisoning have followed the use of tobacco in the form of a poultice applied to local swelling or to stop bleeding, or as an enema. Nicotine is one of the most fatal and rapid of poisons. Two drops may kill a dog in one to two minutes. The *fatal dose* for man is about 60 mg. Death usually occurs in thirty to sixty minutes.

Industrial Nicotine Poisoning.—Nicotine solutions and sprays, used in tanning, as insecticides, etc., have produced poisoning both through inhalation and skin absorption. The symptoms which appear rapidly are vomiting, prostration, stupefaction, cyanosis, tingling and numbness.

The Tobacco Habit

The physician's interest in the tobacco habit is obvious when one becomes cognizant of the following facts: In 1946, the United States manufactured 5,836,344,052 cigars, over 311 billion cigarettes, 211 million pounds of pipe and chewing tobacco, and 39 million pounds of snuff. The cigarettes numbered about 3,300 for every person over fourteen years of age. The consumption of cigarettes has increased from approximately 10 billion cigarettes annually around 1910 to approximately 350 billion annually since 1946. (J. A. M. A. **138**: 653, Oct. 30, 1948.)

Tobacco Smoke

Tobacco smoke is a variable complex substance, some of the constituents produce irritant effects, others initiate marked systemic actions. Those substances producing local irritant action include pyridine bases, formaldehyde and formic acid. Tar and resins found in tobacco smoke are carcinogenic. The most important substances that produce systemic actions are nicotine, carbon monoxide, arsenic, and hydrogen cyanide.

Carbon Monoxide.—The carbon monoxide in tobacco smoke is to be reckoned with. All smoke contains carbon monoxide and a room filled with tobacco smoke is a potential source of poisoning. The drowsiness and headache often complained of after spending an hour or two in a room blue with smoke attests to this fact.

Barach and his co-workers, reporting in the *American Journal of Medical Science* (1941), found that aviators who smoke require more oxygen at a lower altitude than nonsmokers. Cigarette smoke yields 1 per cent carbon monoxide, pipe smoke 2 per cent, and cigar smoke 6 to 8 per cent. Investigators have observed that of 156 officers employed in the Holland Tunnel, where the carbon monoxide concentration averaged 70 parts per million of air, smokers averaged 4.1 per cent to 5.35 per cent blood saturation, while nonsmokers showed only 1.71 per cent.

Arsenic.—All American tobacco contains varying quantities of arsenic because our planters use lead arsenate to kill hornworm parasites. The quantity of arsenic varies, but in the majority of the tobaccos there is fifty times as much arsenic as is allowed in foods by the Pure Food and Drug Laws.

In a report published in the *Journal of the American Medical Association* (1940) Barksdale found that nine brands of cigarettes average

0.0426 to 0.0495 mg. of arsenic per cigarette, two brands of cigars 0.08 to 0.088 mg., respectively; snuff 2.6 mg. per 100 grams, chewing tobacco 1.6 mg. per 100 grams, and smoking tobacco 4 mg. per 100 grams. Tobacco which was untreated by lead arsenate contained no arsenic.

Some *cigarette filters* claim to remove as much as 70 per cent of the nicotine. The laboratory of the American Medical Association confirms the filtering efficiency but goes on to say that the capacity to filter out nicotine is soon lost with use. They also add that the 2 per cent additional combustion afforded by the device partially offsets any filtering advantage. It is interesting to know that cigarette holders favor more complete combustion and thus tend to increase the amount of toxic substances absorbed.

According to the *Journal of the American Medical Association,* if you inhale the *cigarette smoke,* 88 per cent of the nicotine in every cigarette stays inhaled and lodges in your mouth or air passages. Persons who do not inhale, but just puff at cigarettes to be sociable, retain 67 per cent of the nicotine. It concluded that thirty inhaled cigarettes might yield the same amount of nicotine absorption as six cigars smoked without inhaling.

Nicotine Content of Tobacco

The nicotine content of tobacco varies with variety and the manner of curing the leaves. Havana tobacco contains approximately 1.5 per cent nicotine, Virginia tobacco, 6.0 per cent, and Kentucky tobacco, 8.0 per cent. In an average of twenty medium-priced American cigarettes there were 23.85 mg. of nicotine per cigarette, and 11.91 mg. were left in the stub after smoking, according to the studies made by I. H. Pierce and reported in the *Journal of Laboratory and Clinical Medicine* (1941).

There is no relation between the so-called "strength" of tobacco and its nicotine content. Aromatic substances formed during the drying process accounts primarily for the strength. The so-called "denicotinized" tobaccos contain about 1.10 per cent nicotine.

The Effects of Tobacco

The effects of tobacco upon the body may be best divided into acute and chronic intoxication. The latter is of greater interest and importance.

Acute Intoxication

This form of poisoning is seen in beginners who use tobacco, in persons using excessive quantities, and in individuals poisoned by swallowing tobacco or insecticides containing nicotine. The symptoms observed in those just beginning to smoke, or in very mild cases of poisoning, are usually faintness, dizziness, clammy skin, rapid pulse, weakness, faintness, diarrhea, and sometimes nausea and vomiting. The blood pressure rises from 25 to 30 mm. Hg or more above the normal pressure.

The onset of symptoms of severe, acute nicotine poisoning, i.e., swallowing insecticides containing nicotine, is rapid, and death may occur within a few minutes. Nausea and salivation quickly appear and are followed by severe abdominal pain and vomiting. Headache, dizziness, and mental confusion are experienced. The blood pressure may rise and later fall. At first the pupils are constricted, then they become dilated. Collapse may soon follow, with terminal convulsions. Death results from respiratory failure due to paralysis of the muscles of respiration. The usual fatal dose for man is about 60 mg., although 4 mg., or less, may produce alarming symptoms.

Chronic Intoxication

Chronic intoxication usually results from long-continued use of tobacco. The effects are many, and addiction comes eventually with long use. Of great interest and significance is the effect of tobacco in nontoxic quantities over long periods of time. On this subject there is much difference of opinion.

The *heart and circulatory system* are subject to considerable damage by tobacco. All observers agree that changes in blood pressure follows smoking, but there is some disagreement as to what part of the cigarette is responsible. Some blame the paper, some name other ingredients. Dr. Roth and co-workers at the Mayo Institute undertook a series of studies to establish the true cause of the elevation of blood pressure associated with smoking. After performing very carefully controlled experiments on human beings they concluded the following report found in the *Journal of the American Medical Association.*

> "The vascular constriction persisted from half an hour to an hour, in some cases much longer." They further concluded: "These observations make us conclude that the smoking of cigarettes should be avoided in the presence of peripheral vascular disease."

Numerous investigations on the effect of nicotine on the circulation in man have shown that it increases the systolic blood pressure 10 to 25 mm. of mercury and the diastolic blood pressure 7 to 25 mm. of mercury. Herrell and Cusick reported that smoking elevated the average systolic pressure 39.7 mm. Hg and the diastolic blood pressure 28.1 mm. Hg in a series of patients with hyperactive blood pressure. The heart rate was increased 10 to 13 beats per minute by smoking. A prompt fall in surface temperature of the extremities followed the smoking of two cigarettes, and a marked vasoconstriction occurred. In patients with hyperreactive blood pressure smoking produced an average decrease of 22 per cent in the caliber of the retinal vessels. Numerous investigators have reported that the smoking of two cigarettes has precipitated an attack of angina pectoris.

It is difficult to measure the effect of nicotine on the coronary blood flow in man, but investigations have shown that on dogs the blood flow in the coronary arteries is decreased. Glendy and White (1937) compared the smoking habit of one hundred patients under forty years of age, who had coronary disease, with those of patients above eighty years of age and without coronary disease. Fifty-five per cent of the older group smoked as compared to 93.3 per cent of the younger group. Only 4.2 per cent of the older group were heavy users of tobacco, compared with 58 per cent of the younger group.

The *heart and blood vessels* are gradually and slowly damaged by continued smoking. Naturally, the long-continued vasoconstriction and the presence of carbon monoxide produce a general lack of oxygen to various tissues and organs. Coronary heart disease seems ever on the increase in the habitual smoker. This is explained by the repeated and intermittent periods of tachycardia and hypertension that are produced by the nicotine, which overworks the heart. Tice reports four persons with angina pectoris who were relieved on the stopping of tobacco, then upon resumption of smoking died within the hour. Much evidence supports the view that tobacco is the cause of thromboangitis obliterans, a condition characterized by obliteration of arteries of the extremities by thrombi resulting in gangrene.

Temperature Changes.—Drs. Wright and Moffat of New York reported that smoking one cigarette causes a marked drop in temperature

of the fingers and toes. The average drop in a hundred cases was 5.33 degrees Fahrenheit and the greatest drop was 15.5 degrees. They also observed that almost identical effects are produced by various brands of cigarettes, by denicotinized (1.05 nicotine) and by mentholated cigarettes.

With the decrease in temperature there is also a slowing of circulation. This fall in temperature of the fingers and toes, following smoking, is probably due to the same physiological mechanism that is responsible for the relationship between smoking and Berger's disease. In Berger's disease gangrene of a limb occurs as a result of blood vessel spasm and consequently a thrombus formation which blocks circulation. In a large number of patients it was found that 80 per cent were sensitive to tobacco, as compared to 36 per cent of smokers without Berger's disease, and 15 per cent of nonsmokers. Patients with this disease naturally should not use tobacco.

Alimentary tract damage is quite noticeable in chronic smoking. Irritant substances from the smoke and the heat tend occasionally to cause cancer of the lips and buccal cavity. Inflammation of the pharynx passing gradually into the atropic form may occur. Smokers commonly suffer from a chronic inflammation of the stomach mucosa resulting in dyspepsia and probably ulcer. Acid increase is greater in chronic smokers than nonsmokers.

Smoking vs. Respiratory Tract Diseases.—Tobacco smoking causes much harm by producing a protracted inflammatory process from the nose and throat to the small alveoli of the lungs. The most common complaints are chronic rhinitis, laryngitis, and bronchitis.

Pulmonary complications are definitely on the increase in smokers. A mortality rate of smokers taking more than ten cigarettes or one-half ounce of tobacco a day is about six times that for nonsmokers.

Cancer of the lungs is appearing with increasing frequency. Dr. Alton Ochsner of New Orleans, regional director of the American Cancer Society, declared at a recent (1946) medical meeting at Birmingham that men victims outnumber women by five to one, and added that the chain smoker is susceptible to the disease.

Morning cough is perhaps the most familiar symptom of chronic smokers. Dr. Charles S. Hollis commented in the journal entitled *Diseases of the Chest* (1940) that smoking has become so universal and the so-called "tobacco cough" so common that physicians have never generally accepted it as a pathologic entity. "I wonder," Hollis says, "how many millions of cases of permanent physical or mental changes could be tabulated if we were all tobacco conscious to the degree of recognition of this situation when we see it."

The *nervous system* is affected by long-continued use of tobacco manifested by such symptoms as neurasthenia, fatigue, exhaustion, insomnia, and tremor. Amblyopia is an indisputable toxic effect of tobacco. This condition is caused by the chronic spasm of the retinal arteries and results in failing vision and day or night blindness. Complete optic atrophy may occur. Nerve type deafness and ringing in the ears may be present. The most outstanding symptoms are loss of memory, dullness of perception, and slowing of the thinking processes.

The *genitourinary system* is also affected by smoking. There is a mild diuresis resulting from the increase in blood pressure. Later, bladder spasms result in frequency. Heavy exposure to tobacco may cause "tobacco glycosuria." The use of tobacco may initiate and increase uterine contraction even to the extent of causing miscarriage. The fetal heat rate is affected by maternal smoking, and 0.03 mg. of nicotine has been found per liter of mother's milk on a schedule of fifteen cigarettes per day.

Life Span and Smoking

Dr. Raymond Pearl of Johns Hopkins Hospital observed the effect of smoking by study of several thousand nonsmokers, moderate smokers, and heavy smokers. He concluded that, up to the age of forty-five twice as many heavy smokers died as nonsmokers; from forty-five to seventy years the difference was marked but not so great; if the smoker lived until seventy, after that the difference was not great. As one author put it: "He was probably a tough old bird and could take it."

Effect of Tobacco in Pregnancy.—These two facts are indisputable:

1. Nicotine is one of the few substances that passes through the placenta to the fetus.
2. Nicotine passes to the infant by means of its mother's milk.

In view of the virulence of the poison, damage both to the newborn and to the nursing child is inevitable when he is nicotinized before and after birth.

Thousands of experiments have been made upon the progeny of the lower animals, and all record the same result. In 1937, L. A. Pechstein and W. R. Reynolds tested the effects of tobacco on four generations of white rats. Four facts were revealed:

1. The size of the litter was reduced in all generations. In fourth generations the average litter numbered 3.4 instead of the normal 8.5.
2. Many of the young were stunted.
3. Each succeeding generation of smoked-fumed rats became less adept in finding their way out of a maze (a mechanical devise to test the mentality of the rat).
4. The prenatal and postnatal mortality rates were increased from generation to generation, until only 67.6 per cent of those born in the fourth generation survived. The human mother who smokes absorbs much more nicotine into her system than these rat mothers did.

The tobacco habit is one of the strongest of drug habits, for even moderate smokers usually find great difficulty in breaking the habit, and if they suddenly stop smoking they may experience various physical reactions.

Analysis of hundreds of cases has convinced Gray that tobacco-smoking is an etiologic factor in gastric upset. Individual sensitivity, rather than the amount consumed, appears to be the determining factor as regards the symptoms. The therapeutic test for hypersensitivity to tobacco may be of great value in the treatment of many conditions attributable to the use of tobacco.

Treatment.—The symptoms caused by overindulgence in the use of tobacco usually disappear if the use of the drug is stopped. Quick withdrawals do not lead to abstinence symptoms, as with morphine. Some bowel disturbance may occur, and in patients with neurotic tendencies, nervous symptoms may appear.

Lobeline sulfate in doses of 0.008 gram (⅛ grain) orally is not suitable for general use as a "cure" for the tobacco habit, according to Wright and Littauer (1937).

Lobelia and Lobeline

Lobelia consists of the dried leaves and tops of *Lobelia inflata* or Indian tobacco, a weed indigenous in the United States. The chief constituent is the alkaloid lobeline with actions closely resembling those of nicotine. A brand of this alkaloid, "*alpha lobeline*," has been recommended for emergency respiratory stimulation, but safe doses are not reliable and effective doses are not safe. Clinically, the stimula-

tion is transient, and is often associated with nausea and vomiting, sometimes with severe collapse and Cheyne-Stokes respiration.

At present lobelia or its alkaloid is rarely prescribed. The drug is contraindicated as a respiratory stimulant and is worthless as a "cure" for the tobacco habit.

Conium

This drug was formerly used as a sedative and antispasmodic in chorea, mania, convulsions, whooping cough, and asthma; and locally in hemorrhoids and anal lesions. Its peripheral actions are similar to those of nicotine, but it produces more pronounced paralysis of the central nervous system and of the skeletal muscle nerve endings. *Treat* poisoning as for nicotine toxicity.

Gelsemium

Gelsemium is the root of yellow jasmine. It acts similarly to nicotine and coniine. Its central depressant action is relatively more marked. It contains a crystalline alkaloid gelsemine. Gelsemium has been employed in neuralgic conditions, especially trigeminal neuralgia, nervous headaches, hysteria, and similar conditions. The efficacy for the use of this drug is uncertain. Poisoning is characterized by symptoms similar to those of coniine and nicotine. *Treat* as for nicotine poisoning.

Tetraethylammonium Chloride

Tetraethylammonium chloride is a quaternary ammonium compound which blocks the transmission of nervous impulses across autonomic ganglion. Acheson and Moe (1946) first demonstrated this ganglion site of action in dogs and cats. They demonstrated that when the compound is injected intravenously, it provides a prompt fall in arterial pressure in animals in which the pressure is elevated from increasing of sympathetic tone by barbiturate anesthesia.

Decrease in blood pressure caused by tetraethylammonium chloride is rather transient in man. The fall of blood pressure is believed to be due to an increased flow of blood from the arteries because of the diminution in arteriolar constriction controlled by the sympathetic nervous system. In hypertensive patients Lyons et al. (1948) observed a fall of pressure of from 10 to 16 per cent in a large number of patients. They concluded that this agent has no place in daily management of hypertensive patients. *Hypertensive headaches* were often relieved by the drug. In general, 300 to 500 mg. (6 to 10 mg. per kilogram of body weight) were injected intravenously. The oral administration is not satisfactory because of poor absorption in the gastrointestinal tract.

Tetraethylammonium chloride and similar drugs may have a limited usefulness in the evaluation of vasomotor tone and in the symptomatic relief of hypertensive headaches. It is, however, a useful agent in the study of various manifestations of the autonomic nervous system.

References

Autonomic Nervous System

Bard, Philip: Macleod's Physiology in Modern Medicine, ed. 8, St. Louis, 1938, The C. V. Mosby Co.

Brown, G. L.: Transmission at Nerve Endings by Acetylcholine, Physiol. Rev. 17: 485-513, 1937.

Cannon, W. B., and Rosenblueth, A.: Autonomic Neuro-effector Systems, New York, 1937, The Macmillan Co.

Dale, H. H.: Pharmacology and Nerve-endings, Proc. Roy. Soc. Med., 28: 319-332, 1935.
Transmission of Nervous Effects by Acetylcholine, Harvey Lectures, 229-245, 1937.
Eccles, J. C.: Synaptic and Neuro-muscular Transmission, Ergebn. d. Physiol. 38: 339-444, 1936.
Synaptic and Neuro-muscular Transmission, Physiol. Rev. 17: 538-555, 1937.
Nachmansohn, D.: On the Physiological Significance of Choline Esterase, Yale J. Biol. & Med. 12: 565-589, 1940.
New and Nonofficial Remedies, Chicago, 1947, American Medical Association.

Sympathomimetic Drugs

Butler, D. B., and Ivy, A. C.: Method of Application of Drugs to the Nasal Mucosa—a Comparison of Nasal Drops, Sprays and Inhalers, Arch. Otolaryng. 39: 109, 1944.
Edgeworth, H.: Effect of Ephedrine in Treatment of Myasthenia Gravis, J. A. M. A. 100: 1401, 1933.
Ersner, J. S.: The Treatment of Obesity Due to Dietary Indiscretion With Benzedrine Sulfate, Endocrinology 27: 776 (Nov.), 1940.
Feinberg, S. M., and Friedlaender, S.: Nasal Congestion From Frequent Use of Privine Hydrochloride, J. A. M. A. 128: 1095, 1945.
Gunn, J. A.: The Pharmacological Actions and Therapeutic Uses of Some Compounds Related to Adrenaline, Brit. M. J. 2: 155, 1939.
Hartung, W. H.: Inactivation and Detoxication of Pressor Amines, Ann. Rev. Biochem. 15: 593, 1946.
Johnson, C. A.: Ephedrine Sulfate in Treatment of Acute Shock, J. A. M. A. 94: 1388, 1930.
Kully, B. M.: The Use and Abuse of Nasal Vasoconstrictor Medication, J. A. M. A. 127: 307, 1945.
LeCompte, C. B.: Some Clinical Experiences With (oenethyl) 2-methyl-amino-heptane as a Vasopressor Substance, Anesth. & Analg. 25: 168, 1946.
Myerson, A.: The Rationale of Amphetamine (Benzedrine) Sulfate Therapy, Am. J. M. Sc. 199: 729, 1940.
Swanson and Webster: Ephedrine, J. Pharmacol. & Exper. Therap. 38: 327, 1930.
Sympathomimetic Agents—A Symposium, Indust. & Engin. Chem. 37: 116, 1945.

Sympatholytic Drugs

Chess, D., and Yonkman, F. F.: Adrenolytic and Sympatholytic Actions of Priscol (benzyl-imidazoline), Proc. Soc. Exper. Biol. & Med. 61: 127, 1946.
Comfort, M. W., and Erickson, C. W.: Untoward Effects From the Use of Ergot and Ergotamine Tartrate, Ann. Int. Med. 13: 46, 1939.
Nelson, E. E., and Calvery, H. O.: Present Status of the Ergot Question, Physiol. Rev. 18: 297, 1938.
Nickerson, M., and Goodman, L. S.: Pharmacological Properties of a New Adrenergic Blocking Agent; N, N-dibenzyl-β-chloroethylamine (dibenamine), J. Pharmacol. & Exper. Therap. 89: 167, 1947.
O'Sullivan, Mary E.: Termination of One Thousand Attacks of Migraine With Ergotamine Tartrate, J. A. M. A. 107: 1208, 1936.

Nicotine—Tobacco

Bastedo, W. A.: Pharmacology, Therapeutics and Prescription Writing, ed. 5, Philadelphia, 1947, W. B. Saunders Co.

Bogen, E.: Irritant Factors in Tobacco Smoke, California & West. Med. **45**: 342-346, 1936.

Corti, C.: The History of Smoking, London, 1931, George G. Harrap Co., Ltd.

Herrell, W. E., and Cusick, P. L.: Vascular and Retinal Abnormalities Following Inhalation of Tobacco Smoke: Preliminary Report, Proc. Staff Meet., Mayo Clin. **13**: 273-279, 1938.

Hines, E. A., Jr., and Roth, G. M.: Effect of Tobacco on Blood Pressure as Measured by Standard Smoking Test. Proc. Staff Met., Mayo Clin. **13**: 524-526, 1938.

Mendenhall, W. L.: Physiological Effect of Tobacco, Am. J. Physiol. **72**: 549, 1925.

Mendenhall, W. L.: Tobacco, Cambridge, 1930, Harvard University Press.

Pearl, R.: Tobacco Smoking and Longevity, Science **87**: 216-217, 1938.

Schrumpf-Pierron, P.: Tobacco and Physical Efficiency, New York, 1927, Paul B. Hoeber, Inc.

Short, J. J., Johnson, H. J., and Ley, H. A.: The Effects of Tobacco Smoking on Health, J. Lab. & Clin. Med. **24**: 586-589, 1939.

Wright, I. S., and Littauer, D.: Lobeline Sulfate: Its Pharmacology and Use in the Treatment of Tobacco Habit, J. A. M. A. **109**: 649, 1937.

Ziedler, F. A. J., and Wagner, W. J.: Lead and Arsenic Content of Canadian Domestic Tobaccos, Canad. J. Pub. Health **28**: 582-586, 1937.

CHAPTER XIV

DRUGS ACTING ON THE PERIPHERAL NERVOUS SYSTEM

III. CEREBROSPINAL NERVOUS SYSTEM

The drugs acting on the motor nerves of the cerebrospinal nervous system include such drugs as curare, aconite, and others. They are of little clinical importance with the exception of curare. The latter is a useful adjunct to the general anesthetics and is discussed with them.

The drugs acting on the sensory division of the cerebrospinal nervous system include the local anesthetics or those drugs used in regional anesthesia.

REGIONAL ANESTHESIA

The use of regional anesthesia, or anesthesia that is confined to a limited area, has increased greatly in the past score of years.

Historical.—The first introduction of regional anesthesia may be ascribed to Karl Koller in 1884, a Vienna oculist, who accidentally dropped cocaine in his eye and noted the anesthetic effect. In six weeks cocaine was used in America in many cases requiring local anesthesia. In 1884 Halsted (Johns Hopkins) introduced nerve blocking in practical dentistry. Spinal anesthesia was first used by Corning in 1885, and also by August Bier in 1900.

Next in importance was Einhorn's demonstration that esters of aminobenzoic acid have local anesthetic action. His synthesis of novocain (1905) introduced the modern era of local anesthesia.

The third important contribution to regional anesthesia was made by H. Brown (1903), who demonstrated that epinephrine prolongs local anesthesia. The fourth notable contribution was made by Tatum, who presented experimental proof that the preliminary administration of a soporific drug diminished the toxicity of the principal anesthetic.

Methods for Producing Regional (Local) Anesthesia:

1. **Freezing.**
2. Pressure on the nerve trunks and pressure ischemia.
3. Administration of local anesthetic agents. This is usually accomplished by:
   a. Surface application.
   b. Injection anesthesia.
      Injections into or around the nerve trunks.

1. Local Anesthesia by Freezing.—Extreme cold applied locally tends to produce a loss of sensation of the part.

Freezing may be artificially brought about by the use of *ethyl chloride* or by rapid evaporation of ether. With ethyl chloride the evaporation is so rapid that the surface temperature is brought below the freezing point and the area becomes frozen. This freezing acts as a terminal local anesthetic and freezing is indicated by the blanching of the area. This is a convenient method of producing anesthesia for a few seconds only. Prolonged freezing kills the tissues.

More recently (Allen, 1946), *refrigeration anesthesia* was introduced and used for surgery of the extremities. The limb is rapidly cooled from 2 to 8° C. by application of cold. There is a minimum loss of blood and little shock. At this temperature, the activity of the tissues is at a minimum and the spread of infection is halted.

2. LOCAL ANESTHESIA BY PRESSURE.—Pressure on the nerve trunks produces a loss of sensation. A pressure exerted on a superficial nerve may cause local anesthesia, e.g., musculospinal paralysis occurring when an unanesthetized patient's arm is allowed to hang over the edge of the table.

Interference with circulation will cause local anesthesia in the part affected. A certain degree of local anesthesia may be obtained by the employment of an Esmarch bandage. When this bandage is applied by winding about a limb, beginning with the distal end, the limb becomes bloodless or ischemic and is rendered anesthetic to a certain degree.

3. BY ADMINISTRATION OF LOCAL ANESTHETIC AGENTS.—a. Surface application of local anesthetics to mucous membranes, such as those of the nose and throat; for example, solutions of cocaine in strengths of 0.5 to 1 per cent may be applied topically.

Surface anesthesia may also be produced by direct applications of almost insoluble local anesthetics to wound surfaces and mucous membranes, especially of the eye, nose, throat, and urethra.

The actions of the drug depend upon two factors: its power to penetrate mucous membranes, and its power to anesthetize nerve endings. Cocaine, butyn, and nupercaine are effective anesthetic agents on mucous membranes. Procaine has too little penetrative power to be of value on mucous membranes. Alypin and beta-eucaine are intermediate in their absorbability.

Many ophthalmic surgeons prefer cocaine for local anesthesia of the eye; cocaine is reliable and toxic symptoms rarely occur when the drug is properly administered.

For anesthesia of the nose, throat, and urethra, cocaine has an additional advantage of a powerful vasoconstriction action. Unfortunately, out of forty-one deaths due to local anesthetics, twenty followed the application of cocaine to tonsils, and six were due to the use of cocaine in the urethra (Myer, 1924).

Insoluble anesthetics are useful for application to ulcers and wounds. The soluble anesthetics are absorbed too rapidly to be of practical value in pain. On the other hand, the insoluble, slowly absorbed compounds may be useful for wounds and ulcers of skin and mucous membranes. Anesthesin, cycloform, and others are effective on intact mucous membranes.

b. **Injection anesthesia** consists of the injection of a local anesthetic agent into or around the nerve trunk or into the area of nerve distribution, in order to block sensory impulses from the operative area. For this purpose procaine with the addition of epinephrine (1:100,000) is the drug of choice.

Infiltration anesthesia consists of the injection of the anesthetizing fluid around the area to be operated upon in such a manner and in such quantity as to block all the thousands of sensory fibers that lead into it. Procaine in 0.5 per cent strength is most commonly used for infiltration anesthesia. Epinephrine is added to limit rapid

absorption. Cocaine (1/10 to 1 per cent) and quinine and urea (½ to 1 per cent) are also used for infiltration anesthesia.

Large areas can be anesthetized by this method. A sufficient quantity of local anesthetic dissolved in physiological saline is injected in the tissues. A suitable solution is: procaine, 0.1 per cent; sodium chloride, 0.9 per cent; and epinephrine, 0.001 per cent. The pressure caused by the large volume of solution plays a part in the anesthesia, the specific local action of the anesthetic paralyzes nerve endings, and the epinephrine constricts the vessels localizing the action.

Injection into or around the nerve trunks or **conduction anesthesia** is accomplished by injecting the fluid directly into the nerve sheath, or by depositing it immediately against the sheath. When the drug is injected directly into the nerve sheath, anesthesia is immediate and complete in the area it supplies, while by depositing the agent against the sheath, anesthesia is slow, usually incomplete, and of short duration.

Higher concentrations of local anesthetics are needed to paralyze nerve trunks than suffice for nerve endings. Since high concentrations of the local anesthetic are used, it is particularly important not to use a toxic drug. For this reason procaine is the drug of choice. Cocaine is too toxic and is unsatisfactory for this purpose.

General Properties of Local Anesthetic Action.—

1. Local anesthetics probably will not anesthetize intact skin to a great extent, but will anesthetize scarified or exposed nerve ends. On injection of cocaine sensitivity to tickling first disappears, then the sensation of heat, next cold, while touch and pressure are least affected. When action passes off, the sensations return in reverse order.

2. Sensory fibers of mixed nerves, especially the nerve endings, are depressed more than motor fibers. There is evidence that narcosis and analgesia tend to decrease the permeability of the surface layer. This action may be due to dehydrating action on the surface layer. Anesthesia is accompanied by decreased electrical conductivity, and by decrease of the permeability of salts.

3. Adsorption of Positive Ions. A part of the action of an anesthetic is not due to splitting off of a free base but to selective adsorption of the positive ions by negative surface of nerve cells and fibers.

4. Lowering of the Surface Tension. The depression of surface tension runs parallel with anesthetic action.

5. Diffusion and Penetration. Pharmacological action of many drugs varies inversely as the rate of diffusion.

6. Effects of Duration of Application and Concentration. Anesthetic effects vary with length of application and drug concentration.

7. Synergic Action. (a) Epinephrine (1:100,000) increases duration of anesthesia and lowers the threshold of concentration necessary. (b) Lipschitz, Laubender and Weingarten found that salts of caffeine and theobromine, and methylene blue hastened the onset of anesthesia. Caffeine and theobromine increase the penetration rate through the meninges. (c) Narcotics and sedatives potentiate anesthetic action. Antipyrine increases the anesthetic action of cocaine. Acetylsalicylic acid increases the anesthetic action of procaine. (d) The addition of alkali to anesthetic agents increases their efficiency, since free bases penetrate tissues more readily than their salts. This, of

course, would only be of advantage in topical anesthesia. The free bases are insoluble and are impractical for injection. The local anesthetics are usually sold as their soluble salts.

Characteristics of an Ideal Local Anesthetic.—There is no ideal local anesthetic, that is, there is no one local anesthetic possessing all of the desirable qualifications. An ideal anesthetic would have the following characteristics:

1. Specific action.
2. Temporary action.
3. Noninjurious to subject.
4. Freedom from irritating properties.
5. Ability to produce anesthesia for at least thirty minutes.
6. Solubility in water.
7. Ease of sterilization.
8. Relative nontoxicity.
9. Compatible with a vasoconstrictor.

GENERAL TOXICOLOGY OF LOCAL ANESTHETICS

Acute toxicity from local anesthetics is quite frequent, especially with cocaine. A large proportion of the accidents are due to mistakes in the drugs, concentration, and dosage. Idiosyncrasy, differences in absorption, or accidental intravenous injection may also cause toxic reactions.

The usual symptoms of acute toxicity include excitement, anxiety, dizziness, severe headache, convulsions, and fall of blood pressure. Death is due to cardiovascular collapse and respiratory failure.

TABLE XVIII

COMPARATIVE TOXICITY OF VARIOUS LOCAL ANESTHETIC AGENTS

DRUG	SUBCUTANEOUS LD_{50} FOR GUINEA PIGS IN MG./KG. (TOTAL SAFE DOSE FOR HUMANS)
Procaine (Novocaine)	430
Metycaine	300
Tutocaine	190
Butacaine	70
Amydricaine (Alypin)	70
Cocaine	50
Phenacaine (Holocaine)	50
Tetracaine (Pontocaine)	30
Dibucaine (Nupercaine, Percaine)	10

Prophylactic measures include slow injection, the use of dilute solutions, aspiration of syringe to insure that intravenous injection does not occur. Epinephrine (1:100,000) may be indicated to prevent systemic absorption. Preliminary administration of a sedative, especially of the barbiturate group 60 mg. (1 grain) of phenobarbital or 0.6 Gm. (10 grains) of sodium barbiturate one hour before operation, diminishes risk.

Procaine is the safest of the more widely used local anesthetics and may be employed for subcutaneous and submucosal injections; but

the concentration should not exceed 1 per cent. Cocaine and butyn should not be injected under the skin or mucous membranes, but should be restricted to surface application. The total quantity of cocaine should not exceed 0.06 to 0.1 Gm. (1 to 1½ grains). The patient should be recumbent, if the operation permits. With nervous patients, it is advisable to inject morphine fifteen minutes before the local anesthetic, and to delay the start of the operation until twenty minutes after the injection of the local anesthetic. Urethral injections are especially dangerous, and should be avoided if there is trauma or stricture.

Treatment: In general, treatment of acute symptoms of toxicity include stopping the drug and administering barbiturates to control convulsions. Avoid morphine. The injection of epinephrine to combat fall in blood pressure is of questionable value. The use of oxygen and artificial respiration may be indicated. Absorption may be checked by ligation.

If an overdose of local anesthetic has been taken orally, evacuation and chemical antidotes are indicated. Wash out stomach with warm water, keeping this for analysis. Continue with a solution of potassium permanganate (5-10 grains per pint of water).

CLASSIFICATION OF LOCAL ANESTHETICS

Local anesthetics may be classified in various ways: on the basis of their chemical constitution, their solubility, and their clinical use. The latter grouping probably is the most useful for medical students or physicians.

TABLE XIX

LOCAL ANESTHETICS

DRUGS FOR TOPICAL USE ONLY	DRUGS FOR INJECTION ONLY	DRUGS FOR BOTH TOPICAL APPLICATION AND INJECTION
Cocaine	Procaine	Tutocaine
Butesin Picrate	Monocaine	Amydricaine
Butyl Aminobenzoate		Benzyl Alcohol
Ethyl Aminobenzoate		Metycaine
Orthoform		Tetracaine
Amylsine		Dibucaine
Butacaine		
Diothane		
Phenacaine		

LOCAL ANESTHETICS SUITABLE FOR TOPICAL USE ONLY

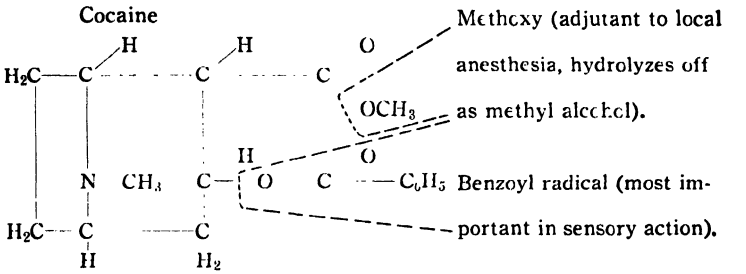
Cocaine

Cocaine is an alkaloid obtained from the leaves of various species of *Erythroxylon coca*, called "Divine plant of the Incas," a plant found in South America and also grown in Mexico and the Indies. Cocaine exists in the dried leaves to the extent of approximately 0.75 per cent. The natives of Peru, who use it, are said to be able to carry heavy burdens for long distances without tiring. Attempts to verify these claims on other races have not been successful.

The local anesthetic properties of cocaine were discovered by Koller (1884), although the drug had been isolated in 1850. Cocaine is now also prepared synthetically.

Cocaine, or benzoylmethylecgonine ($C_{17}H_{21}NO_4$), occurs in colorless, transparent crystals, which are soluble in alcohol (1:15) and ether, but are quite insoluble in water (1:600). It occurs in three isometric forms, *l*-cocaine, *d*-cocaine, *r*-cocaine. The *l* form is of most value therapeutically. The most used salt is cocaine hydrochloride, $C_{17}H_{21}NO_4$·HCl, which is soluble in water (1:0.4), and in alcohol (1:2.6); it is insoluble in oil. If an oily solution is needed, the pure alkaloid must be used.

Cocaine is readily decomposed into several constituents. On heating with water, methyl alcohol is driven off, leaving ***benzoyl-ecgonine,*** which may be broken up into benzoic acid and ecgonine. Recent investigations have shown that boiling cocaine in water for a short time destroys little of the drug for all practical purposes. Aqueous solutions of cocaine salts do not keep well unless sterilized and hermetically sealed.



Ecgonine (stimulates cortex, is responsible for toxic action).

Pharmacological Action.—The most important effects of cocaine are those on the central nervous system and on the sensory nerves.

ABSORPTION AND EXCRETION.—Cocaine is readily absorbed from mucous membranes but is not absorbed through the intact skin. Macht (1916) claims that it penetrates soaked skin. It is eliminated unchanged in large quantities in the urine. The fate of cocaine in man is not entirely known. The destruction of cocaine hydrochloride in the body is relatively slow, which accounts for frequent accidents associated with its use. It is thought that cocaine is first hydrolyzed into ecgonine, benzoic acid, and methyl alcohol, and that these are subsequently oxidized in the body.

LOCAL ACTION OF COCAINE.—Cocaine applied locally on mucous membranes produces a loss of sensation through its paralyzing of sensory nerve terminations, especially those of pain and touch. There is a primary vasoconstriction followed by a secondary dilatation of the vessels. A solution applied to the tongue removes the taste of bitter first, then sweet and acid partially, while the taste of salt remains fairly normal. A solution applied to the nasal membrane completely paralyzes the sense of smell.

Cocaine acts more readily on sensory nerves than on motor nerves. Anesthesia of all the mucous membranes can readily be obtained, but its action on the unbroken skin is less marked, as it penetrates extremely slowly through the epidermis. Hypodermic injections reach the deeper sensory nerves and produce an anesthesia suitable for surgical treatment as long as the knife does not pass beyond the area to which the drug has penetrated.

When cocaine is injected into the region of a nerve trunk, it penetrates into the fibers and induces anesthesia of the region supplied by the nerve. If cocaine is injected into the spinal canal, it causes anesthesia over large areas of the body due to its action on the posterior roots of the cord. The internal administration of cocaine leads to loss of sensation in the mouth and stomach; however, no anesthesia results by its action after it reaches the blood vessels.

Cocaine has a relative selective action for sensory nerves; greater concentrations, however, paralyze motor nerves. When cocaine is applied to the vagus nerve it paralyzes the cardiac inhibitory fibers, while afferent impulses to the respiratory center are more resistant.

Local Action on the Eye.—Cocaine produces a local anesthesia, contraction of the conjunctival vessels, dilation of the pupil, and partial loss of accommodation. The light reflex is preserved. The dilation action may be due to direct action on the muscle fibers of the iris, causing a weakening of the circular fibers, or to stimulation of the nerve ends in the dilator muscle, as does epinephrine; no satisfactory evidence has been supplied.

Eye.—Cocaine, internally or locally, acts as a mydriatic and impairs accommodation. The pupillary mydriasis is not attended with loss of the light reflex, thus indicating that the oculomotor nervous control of the iris is not affected as with atropine. Since cocaine will cause further dilation of the pupil after application of atropine, it indicates that the effect of the cocaine is a stimulation of the dilator nervous mechanism of the iris. The action is peripheral since cocaine dilates the pupil of the excised eye. With large doses there is some contraction of the smooth muscle of the lids, with retraction and exophthalmos. The effect on intraocular pressure varies.

GENERAL ACTION OF COCAINE.—Although cocaine is not administered for its systemic effects, it is absorbed so rapidly that systemic effects may follow its use as a local anesthetic. The systemic effects may be decreased by slow administration of the drug or by the use of epinephrine to delay absorption.

Central Nervous System.—The action of cocaine on the central nervous system is primarily a descending stimulation, the cerebrum being first affected, then the hindbrain and medulla, and finally the spinal cord.

The absorption of small amounts of cocaine first stimulates the cerebrum as shown by wakefulness, talkativeness, and mental keenness. With moderately large doses the reflexes are exaggerated. As the dose is increased, the stimulant effect of cocaine spreads downward to the medulla and cord; this is quickly followed by depression. The depression is manifest in the respiratory and vasomotor centers, and in the reflex centers of the cord. Respiration is increased due to central stimulation. The amount of air inspired becomes less and less, and convulsions may follow. During convulsions respiration becomes irregular, and death may result from paralysis of the respiratory center.

Sympathetic Nervous System.—Some of the sympathetic effects of cocaine, which are similar to those of epinephrine, are attributed to stimulation of the sympathetic nerve endings or to direct action on smooth muscle. The drug taken internally has little effect on the peripheral nerves.

Upon application of a solution of cocaine to a nerve trunk, temporary paralysis is produced, usually without damage if the solution

is not too concentrated. A 2 per cent solution of the drug paralyzes sensory fibers and a 4 per cent solution paralyzes motor nerves, a fact which is ascribed to a greater selective affinity for the sensory class of fibers.

Action on Circulation.—In moderate doses, cocaine accelerates the *heart* by direct action on the cardiac muscle or by stimulation of the accelerator nerve. The *vessels* are contracted in the earlier stages of poisoning, and this combined with the increased heart rate, causes an increase in blood pressure. The constriction of the blood vessels is apparently due to stimulation of the vasoconstrictor center, as it is absent after section of the spinal cord. These actions produce a quickening of the heart rate and a rise in blood pressure. Toxic doses, on the other hand, tend to slow and weaken heart action and cause a fall in blood pressure.

Cocaine, like epinephrine, causes dilatation of coronary arteries. When applied to mucous membrane, the constriction is due to direct action on vessel walls.

Respiration.—Cocaine in full therapeutic doses strongly stimulates the respiratory center of the medulla. The rate of respiration increases and the depth gradually diminishes.

Temperature.—Large therapeutic doses increase body temperature. Reichert states that the increased heat production is due to (1) motor excitement resulting from cerebral cortex excitation, and (2) to direct stimulation of the heat center located in the caudate nuclei.

Alimentary Tract.—Cocaine tends to reduce the appetite, probably by its local anesthetic action in the stomach. This action would also seem to diminish absorption.

Toxicology.—Man is peculiarly sensitive to the general action of cocaine. Furthermore there exists a great variation of susceptibility of individuals to this drug. Most cases of cocaine poisoning have followed its use as a local anesthetic, but occasionally it has resulted from the use of cocaine instead of procaine for infiltration anesthesia.

ACUTE COCAINE POISONING.—Serious acute cases are of two types: (1) the patient apparently suddenly absorbs the drug, becomes pale, gasps, and rapidly passes into a convulsion; (2) the patient becomes talkative, laughs, there is an irregular pulse and respiration, nausea and vomiting, abdominal pain, diarrhea, convulsions, and finally coma and death.

The reactions exhibited are rarely of the purely stimulant or depressant type, but more often are a mixture of both. They may occur rapidly and be difficult to analyze (Tainter).

Treatment of Acute Poisoning.—If cocaine has been accidentally injected, quickly apply a tourniquet above the site of injection but do not completely obliterate the pulse.

In mild cases of poisoning place the patient in a recumbent position and administer rapidly-acting stimulants, such as inhalation of ammonia, hot coffee orally, and camphorated oil or strychnine hypodermically. Since cocaine is quite rapidly destroyed by the tissues, anything that will prolong the life of the patient a few minutes is of great importance.

In severe cases of acute poisoning, when the drug has been taken orally, evacuate the stomach by stomach pump or with an emetic. Give tannic acid (2 Gm.), or strong tea as a precipitant. Chloral hydrate and bromide may be given orally to prevent convulsions. If convulsions occur, administer chloroform or ether, followed by chloral hydrate

(3 to 4 Gm.), and potassium bromide (4 to 6 Gm.). Circulatory or respiratory depression may be combated by stimulants, such as hot coffee by rectum, or caffeine and sodium benzoate (0.3 Gm.) hypodermically. Artificial respiration and even oxygen inhalation may be indicated.

The use of barbiturates both in prophylaxis and treatment of cocaine poisoning has become quite general. Give sodium barbital, 0.4 to 0.8 gram (6 to 12 grains), by mouth, one-half hour before inducing anesthesia. In cases of mild intoxication administer hypodermically 0.1 gram (1½ grains) of barbital. In severe poisoning administer 5 cc. of paraldehyde plus barbital (0.1 gram) intravenously.

Morphine is contraindicated because of its respiratory depressant action.

CHRONIC COCAINE POISONING (Cocaine Habituation).—The habit-forming action of cocaine is an undesirable property of this drug. It is taken for the immediate psychic effects. While the habit is easier to break immediately than the opium habit, relapses are more common. The habit may be either periodical or continuous, or it may be associated with alcoholic or other narcotic indulgence.

On taking a dose of cocaine there is generally a feeling of exhilaration and well-being, accompanied by a quickened pulse, acceleration of circulation, and a remarkable overconfidence in one's mental capacities and physical strength. Occasionally there are vertigo and mental confusion. Many persons show dilated pupils, a rise in temperature, and a loss of the sense of time, though the memory is usually intact. If the dose is not too large, the period of hyperexcitation usually lasts an hour or more but, if the dose is very large, the depression and nervous exhaustion may last for several days.

Diagnosis.—A history is difficult to obtain from an addict. Alternating euphoria and depression, irritation, perforation of the nasal septum and hypodermic scars indicate addiction.

Treatment.—The treatment of cocaine addiction is very difficult for the addict is less conscious of his condition and has less desire to be cured than a morphine addict. The cocaine addict, however, rarely suffers physically from withdrawal as the morphine addict does. When the cocaine habit is combined with the morphine or heroin habit, it should be treated as for morphine or heroin. In most cases cure depends on placing the patient in an institution.

The best procedure is the rapid withdrawal of the drug, but sometimes gradual withdrawal is indicated. The treatment consists of administering an active cathartic, following the last dose of the narcotic. The purgative action will take place after the patient awakens, and it tends to relieve him of some of his nervous condition and to allow further sleep. After this any sedative may relieve the nervousness for several days. The complete cure of the habit from now on requires from six to twelve months of careful supervision.

The treatment is largely symptomatic. Restlessness and insomnia should be combated with barbiturates and bromides, the pains with aminopyrine and salicylates. Active catharsis must be maintained. Scopolamine and atropine have been used to produce amnesia.

Exercise, diet, fresh air, massage and psychotherapy all play an important part in the treatment. The details of each procedure should be worked out to fit the individual patient.

The Towns-Lambert treatment for elimination of narcotic craving has been used with success for cocainism, as well as for alcoholism and morphinism. Briefly it consists of systemic purging, gradually reducing amounts of the drug to which the patient is addicted, and the use of a mixture of two parts of 15 per cent belladonna tincture and one part each of fluidextract of hyoscyamus and xanthoxylum.

Therapeutic Uses.—The therapeutic use of cocaine is based mainly on its ability to paralyze the sensory nerve fibrils on direct application. The preparation most commonly used is cocaine hydrochloride. It is still unsurpassed as an anesthetic application to mucous membrane. For injection purposes it has been replaced by procaine and other agents. When idiosyncrasy is suspected perform the patch test.

LOCAL ANESTHESIA.—Cocaine is indicated, in general, for brief operations in superficial areas of small size, e.g., the amputation of fingers, removal of growths, etc. The chief disadvantage of cocaine is its high toxicity, hence great care must be exercised to avoid overdosage. The maximum dose compatible with safety for adults is placed at 0.03 to 0.04 gram (½ to ⅔ grain).

Preliminary to Instrumentation.—The injection of a few drops of 2 per cent solution of cocaine into the urethra renders *catheterization* painless.

Pharynx and Larynx.—A 10 per cent cocaine hydrochloride spray may be administered once or twice and tested for sensibility with an applicator. When anesthesia is satisfactory, the operation must be rapidly performed, as the period of anesthesia is short. The limit for laryngeal use is placed by some at 0.06 gram (1 grain). A cocaine spray may be indicated *preliminary to taking of food* where pain prevents swallowing, e.g., ulcerations, growths in pharynx, etc.

A 1 to 4 per cent cocaine hydrochloride spray is sometimes used to relieve severe pain which accompanies deglutition in *laryngeal tuberculosis.* This procedure should be used with *caution.* In developed cases of *rabies* 5 per cent cocaine solution will give relief if sprayed into the pharynx.

Analgesia of Ear.—To secure a relative degree of insensibility insert a 10 per cent ointment of cocaine (alkaloidal) in hydrated lanolin; rub in for rapid analgesia, whereas for prolonged action, as in *earache,* it should be just placed in the canal. The following prescription may be used for otitis media:

℞

Atropine Sulfate	0.01 Gm.	(gr.⅙)
Cocaine Hydrochloride	0.20 Gm.	(gr.iij)
Liquefied Phenol	0.60 cc.	(ℳx)
Glycerin q.s. ad	15.00 cc.	(f℥ss)

M. Sig.: Instill five drops in ear as directed.

Eye.—Cocaine hydrochloride is employed before operative procedures, to relieve *pain* in acute inflammation, and in the presence of *foreign bodies.* Solutions of from 0.5 to 4 per cent may be instilled once or more as required.

Solutions of from 2 to 4 per cent produce *mydriatic* action and are of value when pupillary dilatation alone is desired.

To Relieve Congestion and Irritability of Mucous Membranes.—In *acute coryza,* cocaine in 2 per cent solution may be applied or cautiously

used as a spray. In *chronic rhinitis* and *ozena* cocaine carbolate in 1 to 5 per cent solution has been recommended.

In treatment of turgescent rhinitis:

℞

Cocaine Hydrochloride	0.30 Gm.	(gr.v)
Antipyrine	1.00 Gm.	(gr.xv)
Distilled Water q.s. ad	30.00 cc.	(f℥j)

M. Sig.: For use by physician only.

Skin Diseases.—In the theatment of *warts* cocaine hydrochloride may be profitably used for its anesthetic action. A modified paste (Hare) of the following combination may be applied if the warts are few.

℞

Arsenic Trioxide	5.00 Gm.	(gr.lxxv)
Acacia	5.00 Gm.	(gr.lxxv)
Cocaine Hydrochloride	2.00 Gm.	(gr.xxx)
Glycerin	2.00 cc.	(f3ss)
Water q.s.		

M. fac pasta.
Sig.: Apply to warts.

The foregoing prescription may be profitably used in the local treatment of *lupus erythematosus.* The paste is allowed to remain on for twenty-four to forty-eight hours, then the slough is removed by poulticing.

Cocaine may be used in 5 to 10 per cent solutions for preliminary anesthetizing of *chancroid ulcers* before treatment with chemical cauterizing agents.

A 1 per cent ointment of cocaine hydrochloride with equal parts of lanolin and petrolatum relieves the symptoms of *herpes zoster* and causes regression of the eruption.

MISCELLANEOUS USES.—In *hiccup,* Lichenstein (1928) obtained good results by applying a dilute cocaine-epinephrine solution containing a small amount of phenol to both nostrils on pledgets of cotton.

Cocaine in 4 to 10 per cent solution may be used for minor hemorrhages. In the palliative treatment of *hemorrhoids* and *anal fissure,* cocaine is of value as an analgesic and vasoconstrictor.

PREPARATIONS

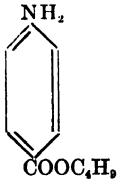
Cocaine, *Cocaina,* U.S.P., B.P. An alkaloid obtained from coca leaves.
Cocaine Hydrochloride, *Cocainae Hydrochloridum,* U.S.P., B.P. *Dosage:* 15 mg. (¼ grain).
Cocaine Hydrochloride Tablets, *Tabellae Cocainae Hydrochloridi,* N.F.

Synthetic Local Anesthetics

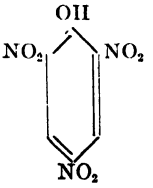
Synthetic local anesthetics have been introduced with the object of finding substances which are nonhabit-forming, less toxic and more stable, and less injurious to the tissues than cocaine. There are now more than one hundred of these compounds. Their anesthetic power is, as a rule, somewhat less than that of cocaine and most of them have the undesirable effect of dilating the blood vessels, and are therefore almost always employed in conjunc-

tion with epinephrine. The most important are based on the discovery that the local anesthetic action of cocaine is due to the radical of benzoic acid in combination with a nitrogen-containing basic group. Important synthetic local anesthetics or cocaine substitutes include the following:

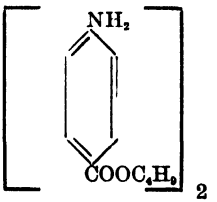
Butesin Picrate, N.N.R., is a yellow amorphous powder soluble in water. It is used in the treatment of burns, ulcers, and other denuded painful lesions of the skin. An aqueous solution (1:2,000)



Butesin
(Butyl Aminobenzoate)



Butesin Picrate

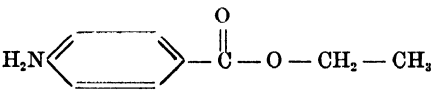


produces immediate and complete anesthesia of the eye which lasts 10 to 20 minutes. For use, a 1 per cent butesin picrate ointment is proposed (N.N.R.).

Butyl Aminobenzoate, U.S.P., is a white crystalline powder soluble in water (1:7,000) soluble in alcohol and fatty oils. It is hydrolyzed slowly on boiling with water.

It is a slow but lasting local anesthetic suitable for topical application to ulcers, wounds, and mucous surfaces. It is used as a dusting powder or in the form of troches, ointments, or suppositories, or in a fatty oil.

Ethyl Aminobenzoate, U.S.P. (Benzocaine), is a white crystalline



Ethyl Aminobenzoate

powder, slightly soluble in water, freely soluble in alcohol. Due to its comparative insolubility, it can be used safely on wounds and ulcers of the skin to induce moderately lasting anesthesia. *Ethyl Aminobenzoate Ointment,* U.S.P., consists of 5 per cent ethyl aminobenzoate in white ointment (95 per cent). In 5 to 10 per cent strength in dusting powder it is applied to ulcers, burns, fissures, and other similar lesions to relieve discomfort. In 10 per cent ointments it is indicated for pruritus. It may be incorporated with other agents in suppositories for relief of pain caused by hemorrhoids or fissures. It may be incorporated in an ointment for the treatment of pruritus in pinworm infection. The following prescription may be used:

℞

Ethyl Aminobenzoate	3.00 Gm.	(gr. xlv)
Salicylic Acid	1.00 Gm.	**(gr. xv)**
Lanolin	15.00 Gm.	**(℥ss)**
Petrolatum q.s. ad	30.00 Gm.	**(℥j)**

M. et fac unguentum.
Sig.: Apply to itching area.

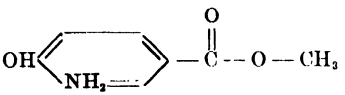
Dr. R. L. Sutton, Jr., recommends the following prescription for chigger bites.

℞

Ethyl Aminobenzoate	2 Gm. (ʒss)
Flexible Collodion	15 cc. (fʒss)

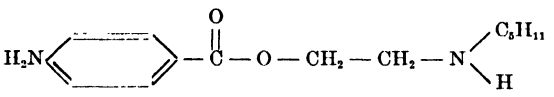
This solution is dispensed in a bottle with a rod in the stopper, and is painted on bites whenever needed. Dr. Sutton claims that it stops the itch for four to eight hours, "enabling the sufferer to sleep at night and to have comparative comfort through the period required for heal ing. It should be used for other bites too."

Orthoform, N.N.R., is a crystalline powder, insoluble in water.



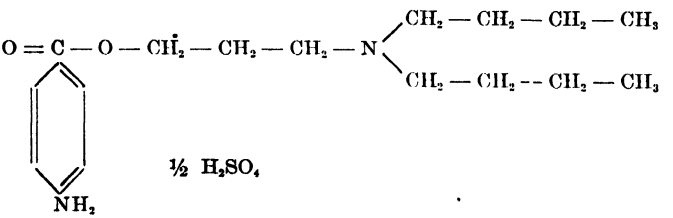
It penetrates the tissues very slowly, and has no action on the unbroken skin. It may be applied locally as an analgesic to various wounds. It has also been used in dentistry, hay fever, nasal catarrh, etc. It is practically nontoxic when used as directed. Its internal use is not advised.

Amylsine Hydrochloride, N.N.R., is a white powder soluble in



water. Its actions resemble those of cocaine hydrochloride but it does not cause mydriasis when used in the eye. Its use probably should be restricted to the production of corneal anesthesia in those cases in which mydriasis is not desired. Toxicity varies widely with the species and mode of administration. One or two drops of a 2 to 4 per cent solution is used in ophthalmology when mydriasis is not desired.

Butacaine Sulfate, U.S.P., is a white crystalline powder soluble

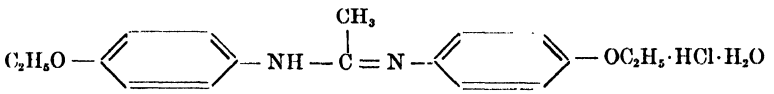


in water (1:1). As an anesthetic to the eye, nose and throat it is usually used in 2 per cent solutions. In the eye, four instillations, three minutes apart, permits operative work within five minutes after the last instillation.

Diothane Hydrochloride, N.N.R., is di-Phenylurethane of 1-Piperidinopropane-2, 3-diol Hydrochloride with actions and uses quite similar to

cocaine, but it is claimed the anesthesia lasts longer. It is quite toxic by vein, thus this route is contraindicated. It is useful for surface anesthesia to relieve pain and irritation in abrasions of skin and mucous membranes following hemorrhoidectomy and for relief of pain in hemorrhoids. A 1 per cent solution is applied to mucous membranes; 0.5 per cent solutions may be injected. It may also be used as a cream for topical application.

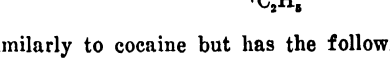
Phenacaine Hydrochloride, U.S.P., is a colorless, crystalline com-



pound, sparingly soluble in water (1:50) and freely soluble in alcohol. It is useful as a local anesthetic, the toxicity being about 50 per cent greater than that of cocaine hydrochloride. It is used mainly for anesthesia in the eye. Installation of 0.3 cc. of a 1 per cent solution in the eye produces anesthesia within one to ten minutes.

LOCAL ANESTHETICS FOR INJECTION ONLY

Procaine *(Novocain).*—Procaine hydrochloride is a synthetic alkaloid which is used as a substitute for cocaine. It is probably the safest of the local anesthetics, especially for injection anesthesia. The chemical formula is as follows:



Procaine acts similarly to cocaine but has the following advantages:

1. No central toxic action.
2. Not habit forming.
3. No liver damage.
4. Not cumulative.

The lack of the ecgonine nucleus in the procaine molecule explains the absence of cumulative action and the lack of liver damage. The drug is very soluble in water, may be boiled, and is compatible with epinephrine.

Pharmacological Action.—The local anesthetic action is less powerful and of shorter duration than that of cocaine. Procaine is relatively ineffective if applied to intact skin or intact mucous membranes.

Procaine paralyzes peripheral sensory nerves as does cocaine. Experiments indicate that it is about one-seventh as toxic as cocaine. Much depends upon its rate of absorption, for, if absorbed slowly, the liver rapidly destroys it. The drug does not produce mydriasis, nor does it constrict capillaries as does cocaine.

Toxicology.—Serious poisoning by procaine is rare; however, mild symptoms of poisoning may occur. These symptoms are weakness, mental confusion or excitement, nausea, pallor, weak pulse, and slowed respiration. Such symptoms may have developed from faulty administration, such as injection of the drug in the vein.

Therapeutic Uses.—The principal use of procaine is to produce anesthesia either by infiltration, or by spinal anesthesia. It is employed in solution in sterile distilled water or with sodium chloride. Epinephrine may be added for its constricting effect.

Intravenous injection of a small amount of the drug is not without danger. Block anesthesia of certain large nerve trunks, such as the sciatic nerve, may require a 2 per cent solution; however, only a small dose of such a concentration can be used. For infiltration anesthesia solutions of 0.25 gram (4 grains) in 100 cc. of physiological saline, with 10 drops of epinephrine solution (1:1,000) are indicated. If a large volume of solution is used, the concentration of epinephrine should be decreased; a total of more than 1 mg. of epinephrine should not be injected in one dose.

Uses in Spinal Anesthesia.—Procaine is considered the least toxic of the spinal agents. Unfortunately, the action is short (55 minutes) when it is given in a safe dose. The effectiveness, however, is a variable factor governed by rates of detoxification and elimination, and by the position of the patient. The usual dose may be determined on the basis of 1 mg. of the drug to each pound of body weight, not exceeding 200 mg.

Some persons are sensitive to procaine, as evidenced by collapse and serious respiratory difficulties. If the blood pressure is low, the drug is contraindicated. Untoward symptoms may be prevented by giving 5 to 10 grains of barbital one hour before administration of procaine.

Pruritus Ani.—Injections with an anesthetic oil containing procaine, such as Morgan's solution, afford relief in many cases. Morgan's solution:

℞

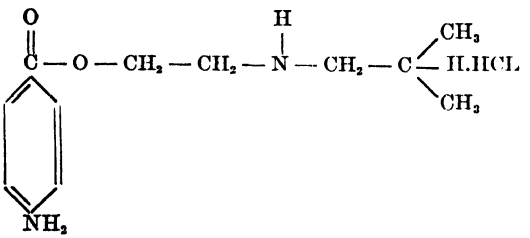
Procaine	1 Gm.
Butesin	6 Gm.
Benzyl Alcohol	5 cc.
Almond Oil	q.s. 100 cc.

M. Sig.: Administer as directed.

Preparation

Procaine Hydrochloride, *Procaine Hydrochloridum*, U.S.P. (Procaine). The total dose varies widely with the purpose for which it is used.

Monocaine Hydrochloride, N.N.R., is a local anesthetic similar to

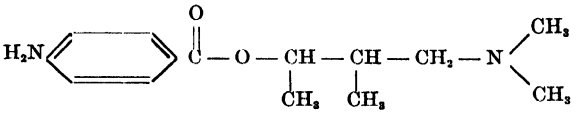


procaine hydrochloride, possessing about one-third more anesthetic and toxic potency. It is used for nerve block anesthesia in dentistry or other surgical operations. It is not recommended for topical use.

For dental or other minor surgery, a 1 per cent solution with epinephrine (1:75,000) may be injected to obtain nerve block anesthesia. In major surgery requiring nerve block anesthesia equivalent to that produced by 2 per cent procaine, a 1.5 per cent solution of monocaine with epinephrine 1:100,000 may be used.

LOCAL ANESTHETICS FOR BOTH TOPICAL APPLICATION AND INJECTION

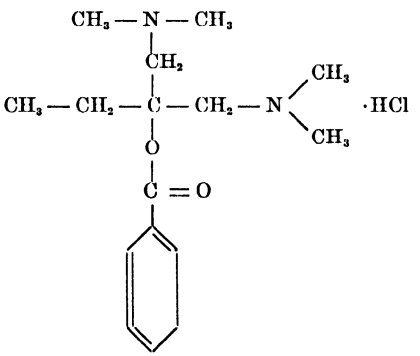
Tutocaine Hydrochloride, N.N.R., is another ester of para-aminobenzoic acid. The base, tutocaine, belongs to the procaine type.



Tutocaine hydrochloride is used primarily for surface anesthesia, but it is also useful for subcutaneous administration. It rapidly produces complete and prolonged anesthesia and is effective in relatively low concentrations. Clinical trials indicate that tutocaine is relatively safe for use in surface anesthesia and also by hypodermic injection.

Dosage: Two to five per cent solutions of tutocaine hydrochloride are used for application to the eye, nose, and throat. For infiltration anesthesia, 0.2 per cent solutions are generally used. Concentrations of 0.5 to 2.0 per cent solutions are indicated for application to the urethra.

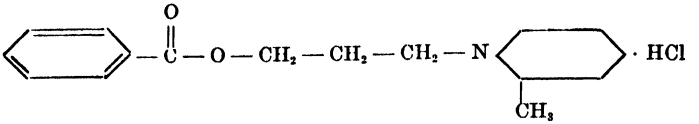
Amydricaine Hydrochloride, N.N.R., is a white crystalline powder



very soluble in water. As a local anesthetic it is equal to cocaine, but is not a mydriatic. It is probably less toxic than cocaine. Reports indicate that severe poisoning can result from its use. In ophthalmology, 2 to 4 per cent solutions are used; in rhinolaryngology, 5 to 10 per cent solutions; in urology, 1 to 4 per cent; in minor surgery, 0.5 to 2 per cent, and in dentistry, 2 per cent solutions.

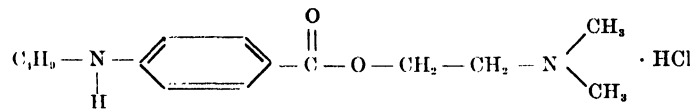
Benzyl Alcohol, N.F. ($C_6H_5 \cdot CH_2 \cdot OH$), is used as a local anesthetic by injection and by application to mucous membranes. Ordinary doses are practically nontoxic and nonirritant. A 1 to 4 per cent solution in water or saline is used for injection. It may be applied topically against pruritus as a 10 per cent ointment; or as a lotion of equal parts of benzyl alcohol, alcohol, and water.

Metycaine Hydrochloride, N.N.R., is a local anesthetic which may



be used topically or by subcutaneous injection. Its toxicity subcutaneously is comparable to procaine; intravenously it is approximately three times as toxic as procaine. For *spinal anesthesia* it is probably equivalent to procaine. Two to four per cent solutions are used for application to the eye; for nose and throat, 2 to 10 per cent solutions; for urethra, 1 to 4 per cent; for infiltration anesthesia, 0.5 to 1 per cent; for nerve block, 1 to 2 per cent; for spinal anesthesia, 1.5 to 5 per cent with a maximum quantity of drug of 0.74 mg. per pound body weight with 150 mg. as an absolute maximum (N.N.R.).

Tetracaine Hydrochloride, U.S.P., is a white crystalline powder

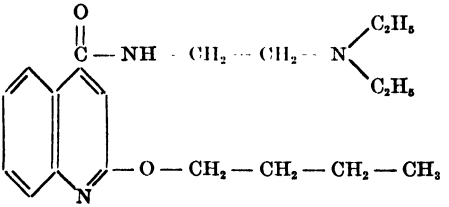


soluble in water and in alcohol. It is a local anesthetic for surface anesthesia in the eye, nose, and throat and in spinal anesthesia. It may be used in lower concentration than procaine.

Solution of 0.5 per cent is used in the eye; a 2 per cent solution for nose and throat; a 0.5 per cent solution for spinal anesthesia. A total of 20 mg. is considered the maximum for spinal injection.

In skilled hands, tetracaine hydrochloride may be used to induce continuous caudal analgesia. (See N.N.R.)

Dibucaine Hydrochloride, N.N.R., is a white crystalline powder,



very soluble in water. It acts like cocaine when applied to mucous membranes, and like procaine or cocaine when injected. The action is relatively prolonged. It is about five times as toxic as cocaine when given by vein, and its anesthetic activity is correspondingly greater than that of cocaine when applied to mucous membranes. It is many times more active than procaine hydrochloride when given subcutaneously.

For infiltration anesthesia, 1 to 2,000 and 1 to 1,000 solution with 0.1 cc. of epinephrine hydrochloride (1:1,000) to 100 cc. of the solution is used. Not more than 100 cc. of 1 to 1,000 solution should be injected. For spinal anesthesia, a total of 7.5 to 10 mg. in 1 to 1,500

solution, which is made by diluting a 1 in 200 solution with an appropriate quantity of spinal fluid. For sacral anesthesia, 25 to 35 cc. of 1 in 1,000 solution is indicated.

SPINAL ANESTHESIA

Spinal anesthesia has gained an important place in the field of medicine, and a knowledge of its technic is essential for every anesthetist. It is really nerve root anesthesia, produced by lumbar or sacral subdural injection of procaine or other local anesthetics, which anesthetize the sensory nerve roots at their emergence from the spinal cord. According to Lundy, the safest agent from the standpoint of experience is procaine, the next is metycaine.

The anesthesia produced by spinal injection of local anesthetics extends to the level of the nerve roots reached by the anesthetic. The aim is to confine the anesthesia to the lower half of the body. If it extends to the fourth ventricle, it paralyzes respiration.

Spinal anesthesia is especially useful in pulmonary disease, in arteriosclerosis, bladder and rectal operations, and in diabetic patients. It should not be used in nervous patients, in children or in very old patients, in the presence of degenerative heart disease or very high or low blood pressure, or in patients with diseases of the central nervous system.

Spinal anesthesia differs from ordinary local anesthesia in the following ways:

1. The injection is made in a diffusible medium, i.e., cerebrospinal fluid.
2. The entire dose is given at once.
3. Nerve cells as well as fibers are exposed to the anesthetic.
4. Loss of motor function and sensory sensation is accomplished, but the appreciation of heat and cold and of pressure and traction is retained (Flagg, 1939).

Advantages of Spinal Anesthesia.—

1. Reduces after effects to minimum.
2. Useful when general anesthetics are contraindicated.
3. Insures a quiet field of operation.
4. No complicated apparatus is necessary.

Disadvantages of Spinal Anesthesia.—

1. Circulatory depression is a common occurrence.
2. Experience is necessary for proper administration.
3. Injection is frequently unpleasant.
4. Persistence of consciousness may be undesirable.
5. A definite dose must be given which cannot be withdrawn.

Spinal Technic.—A perfect horizontal position is gained by placing the patient with his back parallel to, and in close proximity with, the edge of the table. The head should be flexed downward, while the knees are brought upward in full flexion upon the abdomen. If the introduction of the needle is unsuccessful, the patient is placed in an upright position. The back is painted with merthiolate or other satisfactory solutions. A triangular area is then exposed by draping three sterile towels so as to expose the back from the tenth thoracic to the fourth interspace. One is guided in the selection of the site of puncture by the fact that the cord terminates at a level between the first and second lumbar vertebrae. The second or third lumbar spaces are the easiest to tap.

At the site of puncture a solution of 2 per cent procaine mixed with 25 mg. of ephedrine (to maintain blood pressure) is injected into the soft tissue. The lumbar puncture needle is inserted in the usual manner in the second interspace and an injection of 150 to 175 mg. of procaine crystals dissolved in spinal fluid is made.

Some authorities recommend a barbiturate for premedication. Pentobarbital sodium, 3 grains, by mouth the night before, will usually insure restful sleep. Morphine sulfate (⅛ to ¼ gr.) by hypodermic, one and a half hours before operation, is an efficient sedative.

CAUDAL ANESTHESIA

Caudal anesthesia is a special type of peridural anesthesia in which a local anesthetic is introduced through the sacral hiatus into the caudal canal. This type of anesthesia is used in obstetrics and also in surgery.

In obstetrics. Hingson and Edwards introduced continuous caudal anesthesia. In the primipara, caudal anesthesia is begun when the cervix measures 2 to 3 cm., in the multipara the agent is administered somewhat earlier. *Procedure:* The patient is placed in the knee-elbow or lateral flexed position. A 20 gauge intravenous needle is inserted in the middle line through the sacral hiatus. The point is advanced to the level of the third sacral foramen and never higher than the second sacral foramen. The local anesthetics commonly used are metycaine or procaine hydrochloride. Thirty cubic centimeters of 1 per cent in isotonic saline solution is slowly injected about 10 cc. at a time, and an additional 10 cc. if labor pains recur.

The local anesthetic abolishes pain without interfering with uterine movements. It relaxes the cervix which is kept contracted by parasympathetic impulses through the second, third, and fourth sacral nerves (R. A. Hingson, 1944). The average duration of anesthesia is about five hours. The first and third stages are shortened.

Certain advantages are associated with caudal anesthesia in obstetrics. The mother retains consciousness and motor functions; there is no deleterious effect on the vital functions of the child. The rate and strength of the uterine contractions are not interfered with; postpartum hemorrhage is minimized, and management of unfavorable fetal positions is facilitated.

There are certain contraindications to the use of caudal anesthesia in obstetrics. These include sacral deformities, marked disproportion of the child to the birth canal, uterine inertia, extreme obesity, and placenta praevia. Epilepsy, hysteria, advanced anemia, and a history of sensitivity to the local anesthetic may also contraindicate this type of anesthesia.

When properly performed, caudal analgesia is a most satisfactory and pleasant type of procedure. The author has observed Dr. Hingson and his associates administer caudal anesthesia in several instances in obstetrics. No more satisfactory and pleasant type of analgesia could be imagined. It is definitely, however, a hospital procedure and should only be performed in hospitals which have an experienced personnel.

References

Local Anesthetics

Adrian, John: The Physiology of Anesthetic Drugs, Baltimore, 1943, Charles C Thomas.

Beecher, H. K.: The Physiology of Anesthesia, New York, 1938, Oxford University Press.

Brown, H. O., Thomson, J. M., and Fitzgerald, J. E.: An Analysis of 500 Obstetrical Cases With Continuous Caudal Anesthesia Using Procaine, Anesthésiology **7**: 355, 1946.

Burn, J. H.: The Testing of Local Anesthetics, Brit. M. Bull. **4**: 82, 1946.

Flagg, P. J.: The Art of Anesthesia, Philadelphia, 1939, J. B. Lippincott Co.

Hertzler, A. E.: Technic of Local Anesthesia, ed. 6, St. Louis, 1937, The C. V. Mosby Co.

Hirschfelder and Bieter: Local Anesthetics, Physiol. Rev. **12**: 190, 1932.

Lundy, J. S.: Recent Advances in Anesthesia and How They Affect the Surgical Department, Mod. Hosp. **69**: 90-94, 1947.

McQuillen, F. A., and Lundy, J. S.: Trends in Anesthesia as Indicated by a Sampling of the Literature, J. Am. A. Nurse Anesthetists **15**: 187-199, 224, 1947.

New and Nonofficial Remedies, Chicago, 1947, American Medical Association.

Nosworthy, M. D.: The Theory and Practice of Anesthesia, London, 1935, Hutchinson Scientific.

Pitkin, G. P.: Conduction Anesthesia, Philadelphia, 1946, J. B. Lippincott Co.

Refrigeration Anesthesia

Allen, F. M.: Reduced Temperatures in Surgery—I. Surgery of Limbs, Am. J. Surg. **52**: 225, 1941.

Crossman, L. W., and Allen, F. M.: Shock and Refrigeration, J. A. M. A. **130**: 185, 1946.

Melick, D. W.: Refrigeration Anesthesia, Am. J. Surg. **70**: 364, 1945.

Spinal Anesthesia

Hershey, S. G.: Imperfections of Spinal Anesthesia, New York State J. Med. **45**: 1761, 1945.

Maxson, L. H.: Spinal Anesthesia, Philadelphia, 1938, J. B. Lippincott Co.

Seevers, M. H., and Waters, R. M.: Respiratory and Circulatory Changes During Spinal Anesthesia, J. A. M. A. **99**: 961, 1932.

Caudal Anesthesia

Hingson, R. A.: The Control of Pain and Fear in the Management of Labor and Delivery, S. Clin. North America **25**: 1352-1381, 1945.

Lull, C. B., and Hingson, R. A.: Control of Pain in Childbirth, Philadelphia, 1948, J. B. Lippincott Co.

CHAPTER XV

CARDIOVASCULAR DRUGS

Many drugs have the ability to influence the heart and to modify the vascular system. A large number of these agents have as their major pharmacological action the ability to stimulate or depress the heart or to constrict or dilate the blood vessels. This latter group of drugs will be considered in this chapter.

SIGNIFICANT ASPECTS OF ANATOMY, PHYSIOLOGY, AND PATHOLOGY OF THE HEART

It would seem appropriate at this time, before considering the drugs which are of value in the treatment of heart disease, to review briefly the special characteristics of cardiac tissue which may be influenced by drugs, and also to recall briefly a few of the common pathologic conditions which respond to drug therapy.

Significant Characteristics of Heart Muscle.—The heart is the most important muscle in the body and possesses certain remarkable characteristics. Heart muscle possesses those characteristics of all muscle tissue, i.e., *tonicity, conductivity, contractility, irritability,* and, in addition, cardiac tissue possesses the intrinsic power of *rhythmic contraction.*

Tonicity is that property of the heart muscle which prevents complete relaxation during diastole.

Conductivity is that property by which cardiac muscle may transmit impulses along its muscle fibers. Disturbance of this property is a sign of heart block.

Contractility is the property which all muscles possess, namely ability to shorten their length in response to a stimulus. When the property of contractility is damaged, the heart is unable to perform its necessary work.

Irritability is the property of being in a responsive state toward stimuli. Increased irritability is indicated by extrasystoles and paroxysmal tachycardia. Many of the cardiac drugs affect the property of irritability; for example, digitalis increases irritability while quinidine depresses this property.

Rhythmicity is that inherent property of cardiac muscle which enables it to beat regularly. Loss of rhythmicity may interfere with cardiac function.

Nervous Control of the Heart.—The heart beats by virtue of its own intrinsic properties and is capable of beating outside of the body. It is, however, supplied with nerves which, while they do not initiate the heartbeat, they influence it in various ways, according to the needs of the body. These nerves are: (1) the *vagus nerve* (parasympathetic), stimulation of which slows the heart and tends to weaken the contractions, and (2) the *cardio-accelerator nerve* (sympathetic), stimulation of which increases the heart rate and augments the contractions. The heart is also connected by efferent fibers to the medulla; (3) the *depressor nerve,* incorporated in the human being in the vagus, is stimulated by rise of pressure in the aorta, and through its connections in the medulla brings about a fall in blood pressure and a slowing of the cardiac rate.

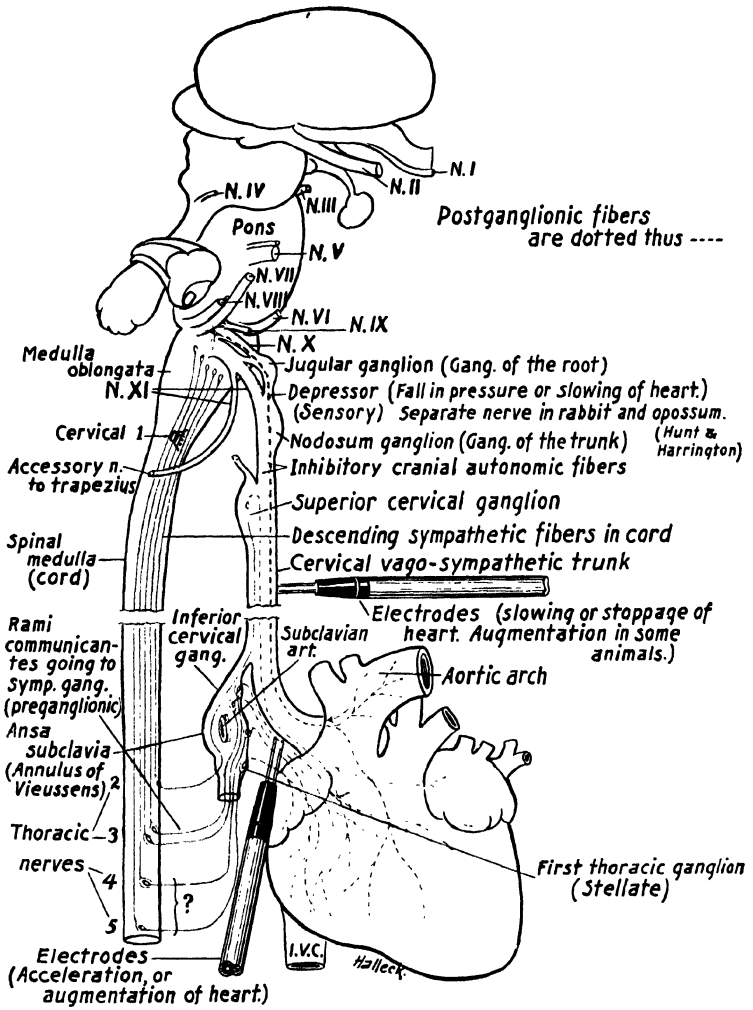


Fig. 18.—Schematic representation of the innervation of the heart. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

Initiation and Transmission of Heartbeat.—The initiation of the heartbeat and its transmission depend on the following specialized tissues:

The sinoauricular node.
The auriculoventricular node.
The auriculoventricular bundle.
The branches of the bundle and the Purkinje system. (Fig. 19.)

The cardiac cycle requires about seven-tenths of a second. Three-tenths of this is taken up by cardiac systole and four-tenths by diastole. The impulse to contraction begins in the sinoauricular node, an area of specialized tissue lying in the right auricle between the openings of the two venae cavae. This impulse is transmitted over both auricles, requiring less than one-tenth of a second, and

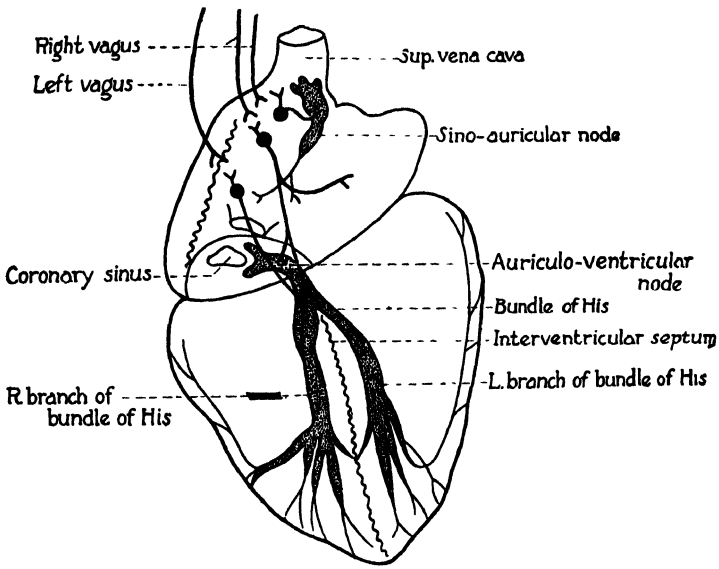


Fig 19.—Diagrammatic representation of the vagus innervation, and of the chief special structures of the heart. (Modified from Wiggers.)

it excites the auriculoventricular node of Tawara, an area of specialized tissue located at the base of the auricular septum. From the A-V node the impulse spreads to the auriculoventricular bundle of His. This bundle passes from the A-V node forward and to the left, to the anterior aspect of the interventricular septum, where it divides into a right and a left branch, passing respectively to the corresponding ventricle. The ventricular divisions break up into a network and pass directly to the cardiac muscle fibers by way of the Purkinje system. The passage of the impulse from the A-V node along the A-V bundle takes about three-twenty-fifths of a second.

The sinus node is spoken of as the pacemaker of the heart. Under pathological conditions the auricles or ventricles may contract independently, due either to locally increased irritability, or to the introduction of an abnormal stimulus (extrasystoles). Independent con-

tractions may also appear with disease of the conduction system. Thus, for example, if there be a complete interruption of the His bundle, the ventricles may beat with their own slow rhythm (about 30 beats per minute), independently of the more rapidly beating auricles.

Although normally the contractions of the heart follow along the path given above, under certain abnormal conditions the auricles and ventricles may beat independently of each other. For example, impulses which may set off partial or complete systole may begin at other than the S-A node. Such impulses may be induced by drugs, such as digitalis or tobacco. Disease may cause degeneration of the auriculoventricular bundle, blocking the normal passage of the impulse.

The Coronary Circulation.—The activity of the heart depends on the energy supplied it by the blood of the coronary circulation. During the greater part of the systole blood is forced from the coronary arteries and during the diastolic pause the coronary arteries refill from the aorta. The heart's activity depends on the efficiency of the coronary circulation. Since the cardiac muscle must undergo rhythmic contraction throughout life impairment of the coronary circulation is quickly reflected as an impairment in cardiac function.

The coronary blood vessels are well supplied with nerve fibers from both divisions of the autonomic nervous system. Experimentation on dogs shows that stimulation of the vagus (parasympathetic) nerve constricts the coronary arteries and that sympathetic stimulation dilates the coronary arteries. It seems probable that the sympathetic dilates the coronary arteries in man. When the coronary circulation is impaired, slowing of the heart rate and allowing longer diastolic rest are beneficial. This accounts for part of the beneficial effect of digitalis in heart failure.

Cardiac Reserve.—The main work of the heart is to pump approximately 100 cc. of blood into the systemic circulation at every beat of the ventricles. As with all other organs of the body, the heart is endowed by nature with considerable reserve, the ability to meet extra strain that may be thrown upon it. As long as the heart can do this, it remains *compensated.* When the burden becomes too great and compensation is broken, heart failure results. Then the heart is *decompensated.* Many conditions, however, decrease the efficiency of the heart muscle and force it to call more and more upon its reserve energy. When the heart is unable to pump sufficient blood into the systemic circulation, the condition is known as *myocardial insufficiency.* The patient develops *cardiac decompensation.*

Disordered Rhythms of the Heart.—*Sinus Arrhythmia* is a condition in which the discharge of impulses begins as usual in the sinoauricular node but, although the strength of the beats is unaffected, their rate varies, generally in accordance with respiration. There is usually an increase in the rate of the heart during inspiration and a decrease during expiration. This is physiological, particularly in young persons; it has no unfavorable significance and does not call for treatment.

Premature Beats or Extrasystoles may arise in any part of the heart and is the result of local hyperirritability.

When a systole occurs, the subsequent normal sinus stimulus occurs during the refractory period, and hence does not cause a beat. The beat caused by the extrasystole is smaller than the normal pulse and may not be felt at the wrist. Extrasystole is the most common form of arrhythmia, and is often due to functional disturbances, tobacco, etc.

Premature contractions are usually not necessarily of serious significance and do not carry a poor prognosis. Sometimes, however, premature contractions are indicative of damaged heart muscle. This type of extrasystole becomes more frequent on exercise, whereas the benign will disappear. Digitalis in full dosage may produce premature contractions. In the presence of digitalis administration premature contractions call for the stoppage of the drug.

Auricular Fibrillation.—This is an irregularity of the heart's action due to irregular impulse formation in the auricle. The auricles beat at a rate of 200 to 350 per minute, but as some degree of heart block is usually present, the ventricles beat at the rate of about 100 to 150 times. Most English and American authors regard auricular fibrillation as the result of a circus rhythm traveling over the auricle in an irregular manner. Continental writers mostly adhere to the idea that it is caused by multiple foci of increased irritability, giving off impulses at an irregular rate and interfering with each other.

The pulse in auricular fibrillation is characterized by complete irregularity. It is almost always rapid. A pulse deficit, the difference between the pulse beats at the wrist and at the apex, is nearly always characteristic of this condition. Digitalis therapy produces miraculous results in this condition. Digitalis or strophanthin acts by creating a block at the auriculoventricular junction, thus protecting the ventricle from the irregular impulses from the auricle. Quinidine sulfate is also of value and acts by reducing the irritability of the heart muscle.

Auricular Flutter.—In this condition the auricles beat very rapidly but regularly. The auricles may contract from 200 to 400 times a minute and about one-half to one-third of these beats get through to the ventricles. It is thought by most authors to be caused by an impulse traveling in a more or less circular course about the orifices of the great veins—a circus rhythm. The ratio between auricular and ventricular beats is usually two to one, with a ventricular rate of from 120 to 170 per minute. Digitalis and quinidine sulfate are also used in the treatment of this condition.

Paroxysmal Tachycardia.—This condition consists of suddenly occurring attacks of very rapid heart action. The attacks have an abrupt beginning and ending, are accompanied by restlessness and exhaustion, and last from a few minutes to several days. During the attack the pulse rate may rise to 140, 160, 180, or more beats per minute. There are two types of paroxysmal tachycardia, the auricular and the ventricular.

An attack may be stopped (⅓ of the cases) by pressure on the vagus or stimulation of the vagus by pressure on the eyeball. Pressure should be applied over the carotid pocket and then followed by pressure over the eyeball. Mecholyl chloride is useful in terminating attacks of paroxysmal tachycardia. Quinidine is of some value in this condition. Digitalis or strophanthin may be used in very persistent cases, but such use is not unattended by danger.

General Methods of Treatment.—The general methods of treatment used in cardiac failure are rest, drugs, and diet. Psychotherapy and removal of focal infection are also important measures used in the treatment of heart disease.

Rest is perhaps the most important single therapeutic measure that can be instituted for the relief of the patient with cardiac disease. Rest, however, to be effective must be complete, mental and physical,

and must be prolonged. In acute heart failure morphine should be used liberally to obtain needed rest.

Diet.—In general, in the presence of heart failure the diet should be somewhat restricted. A fairly balanced diet, with a total caloric value of approximately 1,500, is recommended. It should be made up of vitamins, particularly vitamin B_1. Sodium chloride should be used sparingly. The fluid intake for twenty-four hours should not exceed 1,500 cc. Easily digestible dairy products, chicken, liver, and eggs are to be recommended.

Drugs.—Although rest is the most important therapeutic measure in the treatment of heart failure, many drugs are of value in cardiac therapy. Drugs commonly used in the treatment of cardiac disease include: cardiac stimulants, i.e., digitalis; cardiac depressants, i.e., quinidine. Other drugs, such as the diuretics, morphine, atropine, and the vasodilators may be useful.

THE DIGITALIS GROUP

> "Digitalis treatment is one of the most important and serious duties of the general physician; it demands a great deal of skill, power of observation, keen interest, and experience. A long life is too short to learn enough about this wonderful drug."—Wenckebach.

The "digitalis group" embraces many crude drugs and proximate principles which have a peculiar action on cardiac muscle. Since digitalis is the most important member of this group and possesses the characteristic actions of the group, the drugs are called the "digitalis group" or "digitalis series." Unfortunately, every one of them has many side reactions, no two have the same total constituents or any single constituent in the same proportion. The most important plants belonging to the "digitalis group" are:

- ***Digitalis purpurea*** **(purple foxglove).**
- *Digitalis lanata* and *lutea.*
- *Strophanthus hispidus* or *kombe* (an African arrow poison).
- *Scilla maritima* (squill, or sea onion).

The less commonly known plants of this group are convallaria, apocynum, hellebore, oleander, adonis, and others. The principal source of the pharmacopoeial preparations of digitalis is the leaves of *Digitalis purpurea.*

Historical.—Digitalis was first used as an emetic and diuretic. Withering (1775) showed it to be "specific for dropsy" but did not associate digitalis with heart disease. His "Account of the Foxglove and Some of Its Medical Uses, With Practical Remarks on Dropsy and Other Diseases," appeared in 1785. This account is very interesting and instructive. Many of the principles of modern digitalis therapy are laid down in these pages.

For many years after Withering's death, the use of digitalis was neglected. Scientists of that day observed that digitalis caused an increase in the strength of contraction in the frog heart. They also observed that it prolonged diastole, and that it tended to improve the nourishment of the heart. Traube, Schmiedeberg, and others explained the action as being due to its action upon the inhibitory centers in the medulla.

Early in the present century new methods of study carried out by such men as James Mackenzie, Einthoven, and others have done

much to furnish us with the method of action of digitalis in heart disease. Mackenzie elucidated its beneficial effect in auricular fibrillation. In 1903 Einthoven began his epoch-making studies of the electrical mechanism of the heartbeat with a delicate string galvanometer. The correct understanding of the action of digitalis was greatly aided by the use of this apparatus.

Properties of Digitalis Group.—The digitalis group embraces many crude drugs and proximate principles which have a characteristic action on the heart muscle. Most of the principles found are derived from digitalis, strophanthus, and squill.

Digitalis and digitalis-like principles may be administered by mouth or injection. Although the cardiac action of the group as a whole is quite similar, wide differences exist in regard to their absorption, cumulative action, and emetic action.

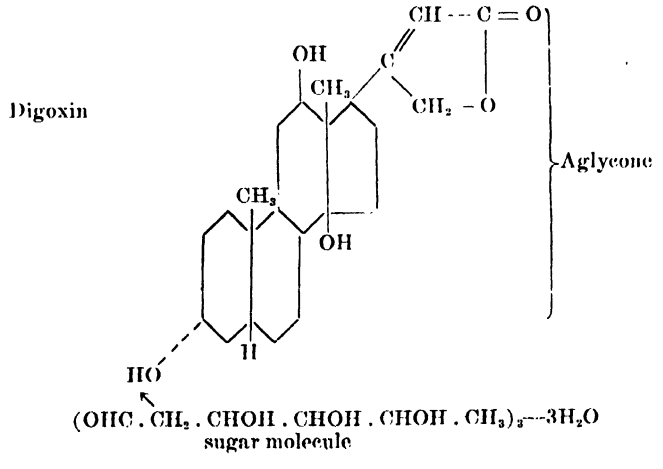
Digitalis contains a mixture of glycosides, some of which are rapidly and others poorly *absorbed* from the gastrointestinal tract. After an oral dose of digitalis leaf, about one-fifth of the potent principles are absorbed, as shown by the fact that it requires about one-fifth as much for intravenous as for oral administration to produce the same results (Gold, 1947). Whereas about 20 per cent of preparations of digitalis leaf is absorbed in the gastrointestinal tract, practically 100 per cent of digitoxin is absorbed. It has been shown that about 10 per cent of an oral dose of lantoside C. is absorbed from the gastrointestinal tract. The potent principles of strophanthus are so poorly absorbed that they are undesirable for oral use and are used chiefly by intramuscular or intravenous injection.

All the digitalis bodies are cumulative, but do not show the same degree of cumulation. This action is especially pronounced in case of the digitalis leaf and digitoxin, while it is much less with strophanthin.

The frequency of repetition of the intravenous dose of the various digitalis preparations vary widely, even with those of equal potency.

Cardiac Glycosides

There are sixteen or more glycosides in digitalis. The three which have been isolated chemically pure from the dried leaves of the official *Digitalis purpurea* are digitoxin (crystalline), gitalin



(amorphous), and gitoxin. Digitalis also contains saponins (digitonin, digitsaponin, and gitonin), which do not produce the typical cardiac effects, but which probably modify the solubility of the other principles. The cardiac glycosides are conjugation products of sugars and nonsugars. The nonsugar portions are known as *aglycones* or genins, closely related in the different principles of the various plants, composed of a cholanic (cyclopentane phenanthrenic) nucleus with seventeen carbons and an unsaturated lactone side chain with four or five carbons which are essential to its action.

The aglycones (or genins) are chiefly responsible for the digitalis actions. The sugars influence penetration. The aglycones are generally less active on the cardiac muscles than are the corresponding glycosides. The glycosides, however, possess a long persistent action, and are characterized by a latent period before they act.

As previously mentioned, digitoxin, gitoxin, and gitalin have been isolated from *Digitalis purpurea*. On complete hydrolysis, they give the aglycones—digitoxigenin, gitoxigenin, and gitaligenin. (Table XX.)

TABLE XX

CHEMICAL RELATIONSHIPS OF THE GLYCOSIDES OF DIGITALIS PURPUREA

Purpurea glycoside A	-glucose	Digitoxin	-3 digitoxose	Digitoxigenin
Purpurea glycoside B	-glucose	Gitoxin	-3 digitoxose	Gitoxigenin
Glycoside ?	-?	Gitalin	-2 digitoxose	Gitaligenin

Three glycosides have been isolated from *Digitalis lanata*, lantoside-A, lanatoside-B, and lanatoside-C, which on partial hydrolysis yield digitoxin, gitoxin, and digoxin, respectively.

TABLE XXI

CHEMICAL RELATIONSHIPS OF THE GLYCOSIDES OF DIGITALIS LANATA

Lanatoside A	-(CH_3COOH glucose)	Digitoxin	-3 digitoxose	Digitoxigenin
Lanatoside B	-(CH_3COOH glucose)	Gitoxin	-3 digitoxose	Gitoxigenin
Lanatoside C	-(CH_3COOH glucose)	Digoxin	-3 digitoxose	Digoxigenin

Digitoxin is probably the most important principle of the digitalis leaf (0.20 to 0.40 per cent). This principle does not occur in the seed. It was isolated by Nativelle (1869). Digitoxin occurs as crystals, is soluble in alcohol and in chloroform, and difficultly soluble in water when pure. Its solubility, however, is greatly modified by the presence of other principles, especially the saponins.

Gitalin, the amorphous digitalis principle, is soluble in water and more soluble in chloroform. It is about 360 times as potent as digitalis leaves.

Gitoxin has also been isolated and its formula established.

Action on Myocardium.—Digitalis action on the heart muscle is of greatest therapeutic importance. Such observers as Christian (1919), Luten (1924) and others, hold that digitalis is of value in

congestive heart failure by virtue of its direct action to increase the force of myocardial contraction rather than due to its action on cardiac rhythm.

Digitalis acts on the cardiac muscle to increase the force of systolic contraction. This causes the ventricles to empty more completely, and the heart is thus enabled to handle an increased venous return. If the venous pressure is high due to congestive failure, this pressure is lowered.

1. *Action on Heart Rate.*—Therapeutic doses of digitalis produce no significant slowing of heart rate in the diseased or normal heart. Congestive heart failure in man is often relieved by digitalis without evidence of cardiac slowing. Furthermore, if slowing does occur, it usually occurs some time after beneficial results have been observed. *Thus one must conclude that improvement in heart failure is not dependent primarily on cardiac slowing.*

2. *Action on Conduction System.*—Slowing of conduction between the auricle and ventricle occurs in both normal and decompensated hearts following therapeutic doses of digitalis. A prolongation of the auriculo-ventricular interval to three-tenths of a second may result from digitalis. This effect is best determined by the "electrocardiogram" and indicates stoppage of the drug. If slowing does occur it is partly vagal in origin but mainly is due to direct action of digitalis on the conduction bundle. These factors may tend to hinder the auricular impulses from reaching the auricle.

3. *Tonicity and Contractility.*—Digitalis has an important effect on the tonicity and contractility of the myocardium. By tonicity of muscle we mean its property of maintaining a state of partial contraction during its resting period, while by contractility we mean its power to contract against resistance. In a heart with hypotonicity and hypocontractility the ventricular chambers are dilated and weak, so that in diastole the muscle is stretched beyond the normal by the venous inflow, and in systole is contracted feebly. This results in a decreased output of blood. With digitalis there is produced an *increased contractility of the cardiac muscle,* accompanied by more powerful and prolonged contraction. Besides the increase in contractility there is also a tendency toward the *restoration of cardiac tonus.* Under such conditions there is an increase in blood flow, although the cardiac rate with sinus rhythm is unaltered. The fluoroscope may even reveal a decrease in size of the heart and a marked ventricular contraction.

4. *Irritability.*—Digitalis increases the irritability of the heart, producing a condition of overexcitability of the myocardium which often results in auricular or ventricular premature beats, and in high overdosage paroxysms of ventricular tachycardia, auricular or ventricular fibrillation, and auricular flutter. If auricular or ventricular fibrillation does occur, the patient usually dies eventually as the result of ventricular fibrillation.

5. *Action on Heart Size.*—Careful study of roentgenograms indicate that both normal and decompensated hearts decrease in diastolic size following digitalis therapy. This decrease in size has been attributed to various factors. Some attribute it to an increase in tone, others ascribe it to an increased systolic force of contraction. Space will not allow detailed discussion of this question.

THERAPEUTIC BENEFIT FROM DIGITALIS is achieved in one or all of the following ways according to Stroud (1940):

1. By slowing the heart rate, that is, by lengthening the number of ventricular systoles per minute, the diastolic period is lengthened,

whereby ventricular filling is rendered more complete, and the heart muscle fibers are afforded more rest. Therefore, greater expulsion of blood into the circulation with each systole may result.

2. By increasing the cardiac tone, thereby relieving or preventing dilatation of the heart chambers beyond the physiologic unit, the optimum cardiac output is made possible. When the length of the heart muscle fibers is increased beyond a certain limit, the cardiac output is decreased and "heart failure" is believed to result. Restoration of the fibers to a shorter length is a factor in bringing about an increase in cardiac output, with the possible return of circulatory efficiency.

3. Through increase of the extent of ventricular contraction, there tends to be an increase in cardiac output when heart failure is present.

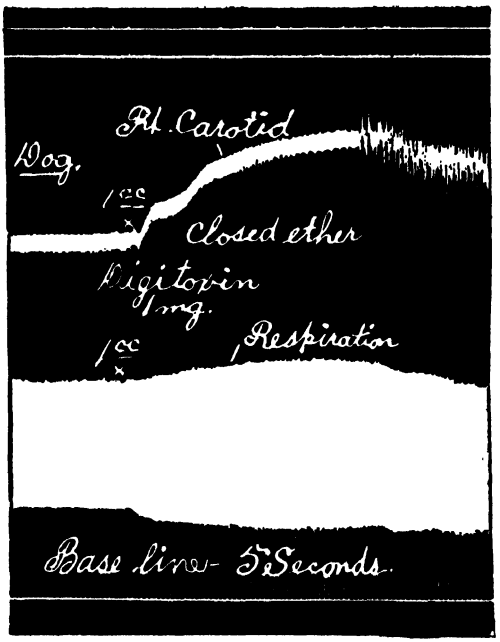


Fig. 20.—Tracing showing the action of 1 mg. of digitoxin on the blood pressure and respiration in a dog. Slow drum. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

ACTION ON BLOOD VESSELS.—For years, controversy has existed as to whether or not digitalis has a direct effect on the blood vessels of man. Eggleston (1917) after reviewing the literature on this subject indicated that the bulk of the evidence is against such action. Pharmacological investigations have demonstrated again and again, however, that in animals digitalis in large amounts causes a constriction of the arterioles. This is due mainly to the direct action of the drug upon the muscle in the vessel wall.

Effect on Coronary Arteries.—There is a great deal of evidence to show that digitalis has a tendency to constrict the coronary vessels; many deny this tendency. In summarizing the results of experimental

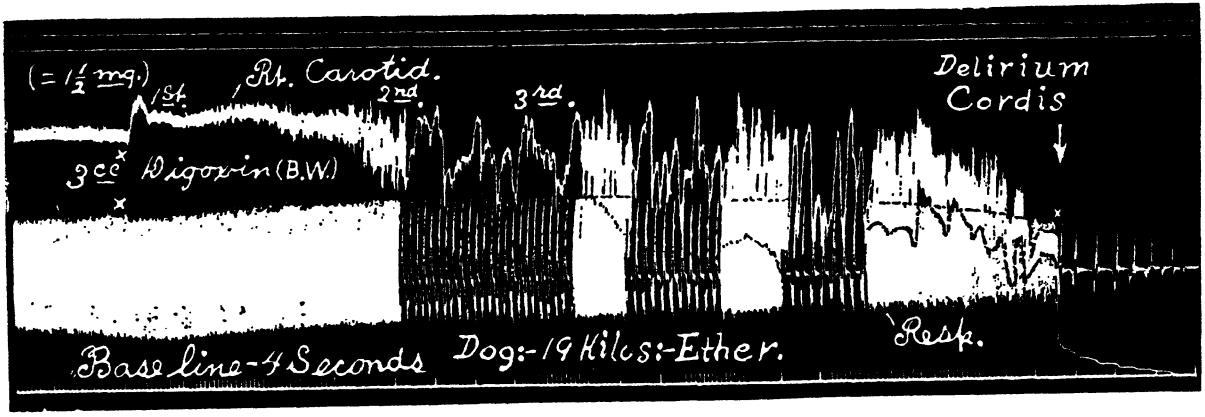


Fig. 21.—Blood pressure and respiration showing the action of digoxin. Note the final delirium cordis. The three stages of digitalis action are shown. At intervals the drum was run fast to show the variations in heart action. Note that the irregularities in blood pressure do not correspond to any changes in respiration, but that they are dependent entirely on the arrhythmia of the heart. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

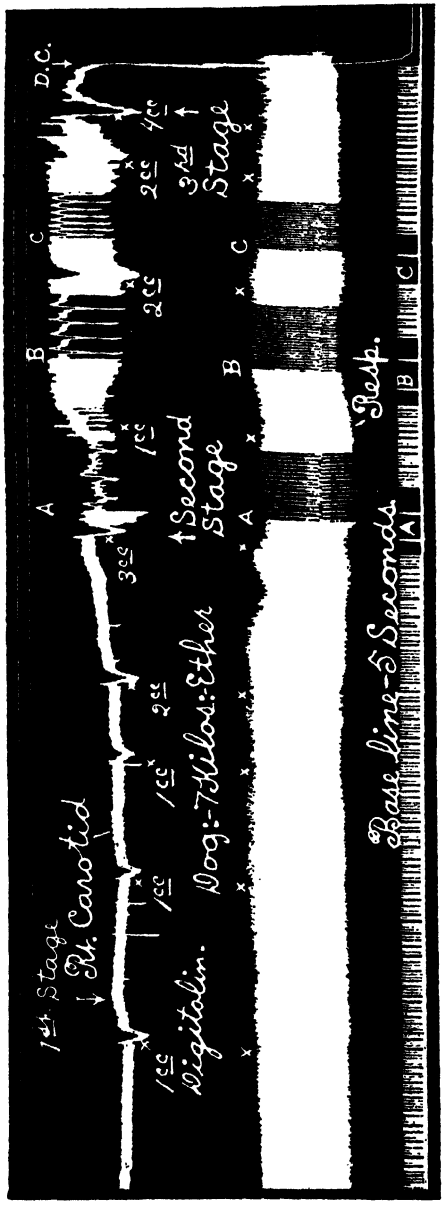


Fig. 22.—Blood pressure and respiration showing the action of digitalin. The three stages are shown and also the fatal delirium cordis, *D.C.* (ventricular fibrillation). Note that the pressure falls to zero at once when the ventricles start to fibrillate. At three places the drum was run at great speed to show the irregularities of the blood pressure (*A, B, C*). The first is the therapeutic stage. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

work with digitalis Cushny's (1925) conclusion was: "In the smaller quantities used in therapeutics, digitalis has not been shown to affect coronary circulation."

Effect on the Hepatic Vein.—Dock and Tainter (1930), using "full therapeutic doses for man," concluded that digitalis causes a constriction of the hepatic vein in normal dogs. They believe that the diminution of cardiac output observed in normal men may be partly accounted for by a lessened inflow so produced. The validity of their conclusions has been questioned by some in view of the fact that in human beings the hepatic vein possesses but little smooth muscle.

ACTION ON BLOOD PRESSURE AND RESPIRATION.—Experimental results seem to indicate that in normal men therapeutic amounts of digitalis exercise no great effect on blood pressure. Experimental administration of digitoxin to dogs shows a rise in blood pressure accompanied by an increase in depth of respiration. (Figs. 20, 21, and 22.) The rise is due partly to the increased output of the heart, but mainly to vasoconstrictor action of the arterioles, especially of the intestinal vessels. Available clinical evidence substantiates this view. There is probably a tendency for the systolic pressure to rise, but this may be more than compensated for by reflex adjustments. The rise, when it does occur, occasions no great concern and constitutes no contraindication to the administration of the drug to patients with hypertension.

ACTION ON KIDNEYS.—Digitalis was first used as a diuretic. It is now thought to have little direct action on the kidneys, the diuresis being accredited to improved circulation. On the other hand, Cloetta feels that digitalis is a true diuretic with specific action on renal epithelium. Withering used it only in dropsy cases, not recognizing its heart action at the time. Although the question is still open for investigation, many feel that the diuretic action is secondary to the improved blood flow. Clinically, however, diuresis occurs only in congestive heart failure and does not follow the administration of digitalis in normal individuals, nor in patients with edema due to nephritis not associated with heart failure.

The diuretic action is summarized by Eggleston as follows: "It is clear then that the diuretic action of digitalis in man is essentially secondary to its capacity to relieve heart-failure and restore the circulation; and when it is effective in edematous cases of heart-failure, it is often one of the earliest manifestations of the action of the drug, though other evidences can be detected if looked for."

ACTION ON THE GASTROINTESTINAL TRACT.—*Anorexia, nausea,* and ***vomiting*** are common gastric symptoms associated with digitalis therapy. Diarrhea occurs occasionally. Vomiting, which is often preceded a few days by anorexia, may be considered a valuable sign of digitalis toxicity, and is a warning that the drug should be stopped.

The emetic action may be attributed in part to the irritant action on the gastric mucosa, and also in part to the vomiting center (Hatcher and Eggleston). The seat of this action also is thought to be the heart. The emetic action is roughly proportional to the cardiac effects of the various members of the digitalis group and when this undesired action is induced, it cannot be avoided by changing the route of administration or by trying other members of the group. In such a case the patient is overdigitalized and the size of the dose should be reduced.

ACTION ON CENTRAL NERVOUS SYSTEM.—The action of digitalis in therapeutic doses is confined largely to the stimulation of the vagus center. Toxic doses may stimulate the vasoconstrictor and respiratory centers, and occasionally the vomiting center. The cerebrum may be

stimulated by increased circulation. Headache, drowsiness, mental confusion, and visual disturbances are common manifestations of digitalis poisoning. The bulk of the evidence indicates that vomiting is reflex in origin.

Toxicology.—Poisoning by digitalis is usually due to accidental therapeutic overdosage. Fatalities rarely occur with divided doses by mouth. Usually, death has been due to a single massive dose or to large doses intravenously. Suicidal and homicidal cases are rare. Occasionally digitalis has been taken during military service for the purpose of malingering.

Every physician should understand the toxic effects of digitalis. The earliest symptoms of digitalis poisoning are *nausea* and *vomiting*, the vomiting frequently being preceded by a day or more of anorexia, headache, and vertigo. All active preparations of digitalis will cause gastric disturbances. In patients who are seriously ill the range between the therapeutic dose and the toxic dose seems so narrow that effective doses are usually attended by nausea and vomiting. In severe congestive heart failure vomiting may be associated with severe splanchnic congestion and not be due to digitalis. Vomiting of this type usually occurs shortly after administration of digitalis and disappears with improvement of heart action.

The following is a list of important toxic manifestations which may be associated with digitalis therapy.

Gastrointestinal:	Nausea, loss of appetite, vomiting, diarrhea.
Circulatory:	Extrasystoles, coupled rhythm, ventricular tachycardia, partial or complete heart block, stimulation of any of the other spontaneous arrhythmias, diminution in secretion of urine, cold extremities.
Nervous:	Headache, drowsiness, mental confusion, visual disturbances.

Patients receiving digitalis are usually sensitive to *epinephrine* and to *intravenous calcium*. These drugs should be avoided during digitalis therapy.

The *postmortem findings* are not characteristic. It is impossible to estimate what amount of digitalis preparation constitutes a *fatal dose*, since it depends on the rate of absorption, upon recent administration, and upon individual reactions. Records show 2.5 grains have caused death. The *fatal period* is usually two days, but may be prolonged to two weeks. There are reported cases of poisoning from 1 mg. of strophanthin administered intravenously.

Treatment.—Signs of toxicity require that digitalis be stopped for twenty-four hours or until these signs disappear. Toxic effects can be minimized by smaller doses, by longer intervals between doses, and by more accurate knowledge regarding previous digitalis medication. If the poison is still in the stomach, remove it by emetic or gastric lavage, with potassium permanganate, 0.1 per cent (1:1,000), or tannic acid, 1 per cent. An ice cap, or hot water bottle, may give relief to palpitation of the heart. The patient must be kept quiet and warm. Atropine, sodium nitrite, and quinidine are of no value in the treatment of digitalis poisoning; atropine will not abolish severe irregularities, nitrites may accentuate a partial collapse, and quinidine is actually dangerous in digitalis poisoning. In severe cases the blood pressure is likely to be lowered, but the idea that local vasoconstriction in the cerebral or coronary vessels may occur has no basis. Sodium bromide or sodium phenobarbital may be indicated to counteract the excessive irritability.

Digitalis Therapy

The Foxglove's leaves, with caution given,
Another proof of fayouring Heav'n
Will happily display;
The rapid pulse it can abate;
The hectic flush can moderate
And blest by Him whose will is fate,
May give a lengthen'd day.

William Withering.

No more fascinating chapter in medical history has been written than that of the changing notions through the years concerning digitalis therapy. The drug has been used as an emetic, as an expectorant, as a specific for phthisis, and by Withering in cardiac dropsy. References to the literature of a few years ago make it apparent that our ideas in regard to the indications and the contraindications of digitalis therapy are rapidly changing and at present leading opinion on the subject is not uniform. There is little question, however, but that digitalis is the most important drug in the treatment of heart failure.

Digitalis is especially useful in the following conditions:

1. Congestive heart failure.
2. Auricular fibrillation.
3. Auricular flutter.
4. Tonic doses for mild cardiac improvement associated with renal disease and the senile heart.
5. As a therapeutic test to detect mild congestive failure.

1. CONGESTIVE HEART FAILURE.—Digitalis administration should be begun immediately. In failure with regular rhythm, the digitalis acts primarily on the heart to increase force and efficiency of contraction. It may act, in part, to constrict the hepatic veins, decreasing venous return to the already embarrassed heart. If due to auricular fibrillation or flutter, digitalis acts additionally by increasing the degree of heart block and, thus, slowing of the ventricles.

Administer a large dose of digitalis over a brief period to saturate the patient quickly to a therapeutic level. Then give a sufficient dose to maintain the proper concentration. If the powdered digitalis leaf is used, about 1 to 1.5 Gm. may be needed to saturate an adult when given over a forty-eight-hour period. Administer in divided doses: 0.4 Gm. for initial dose, and 0.2 Gm. every four hours thereafter for three or four doses until patient shows improvement.

More recently, purified glycosides of digitalis have been found satisfactory for clinical use. Digitoxin may be administered orally, giving a full digitalizing dose, 1.2 mg. ($\frac{1}{50}$ grain), of digitoxin with minimal prospects of gastrointestinal irritation by virtue of the small bulk of drug required to produce the desired effect. The daily *maintenance dose* is usually 0.2 mg ($\frac{1}{300}$ grain). In a few patients 0.1 mg. is satisfactory, and some of the more tolerant patients require as high as 0.3 mg. or more daily.

It is seldom necessary to administer digitalis parenterally. If vomiting is present, or if the situation is so grave that prompt action is required, administer a digitalis glycoside by vein. Since ouabain, when given intravenously, attains its full effect in two hours, it is the preparation of choice. An initial dose of 0.3 mg. ($\frac{1}{200}$ grain) given intravenously may be followed by intravenous injections of 0.1 mg. ($\frac{1}{600}$ grain) at intervals of two or three hours until a satisfactory therapeutic

effect is attained. Bear in mind that a dose of three to five cat units of lanatoside C, or digitoxin, will produce a satisfactory digitalis effect when given intravenously but the action of these compounds is less prompt than that produced by ouabain when similarly administered.

Other specific measures must not be neglected in the treatment of acute heart failure. *Morphine* (10 to 15 mg.) may be indicated to quiet the patient, also to slow respiration and decrease dyspnea. *Venesection* with removal of 500 to 700 cc. of blood may be a second valuable measure. Inhalation of oxygen may be indicated to supplement the treatment.

2. AURICULAR FIBRILLATION.—Striking results follow the use of digitalis in the treatment of auricular fibrillation and the reputation of digitalis as a remedy for cardiac disease was due chiefly to its beneficial action in this type of arrhythmia.

To understand the action of digitalis in this condition we must remember that in auricular fibrillation there is a self-perpetuating ring of excitation about the mouth of the vena cava in the right auricle resulting in a rapid, incoordinated auricular action of from 400 to 600 beats per minute and a ventricular rate of from 90 to 100 beats per minute. In this condition digitalis is used to obtain a restraining effect upon the conduction time between auricle and ventricle, i.e., to produce a partial heart block so that the abnormally great number of impulses from the fibrillating auricles can reach the ventricles only at longer intervals. The ventricle is therefore slowed down and steadied, and as a result the heart's action becomes more efficient and circulation improves.

Digitalis should be given in auricular fibrillation in full therapeutic doses. In this condition digitalis therapy usually has to be continued indefinitely. The effect of digitalis upon these cases is miraculous. The ventricular rate falls rapidly, the urinary secretion increases, and consequently dropsy disappears; the dyspneic condition improves and after a few weeks the patient is able to be up and around, and may even do light work.

Young patients with auricular fibrillation usually respond more favorably to digitalis than do older arteriosclerotic patients. This can, no doubt, be attributed to the impairment of conduction between the auricles and ventricles often present in older patients, and to the presence of pathological changes in the myocardium.

A fibrillating heart may be seriously damaged. When the damage is slight, and especially in the fibrillation of hyperthyroidism persisting after thyroidectomy, an attempt to restore regular rhythm may be made, using quinidine sulfate.

3. AURICULAR FLUTTER.—Auricular flutter is much less common than auricular fibrillation but is of somewhat similar physiological nature. In auricular flutter the auricle usually beats about 300 times per minute, while the ventricle responds to every two or three auricle beats. The response of the ventricle may differ in different patients or even in the same patient at different times; sometimes the ventricles may respond to every beat of the auricles, sometimes to every other beat, sometimes to every third or fourth beat.

Full digitalization should be instituted at once in order to block the bundle of His and protect the ventricle from rapid stimuli coming from the auricle. Digitalis is of value because of its ability to transform flutter to fibrillation in many instances, with restoration of normal rhythm on discontinuing its use. If there is a likelihood that the arrhythmia may return, quinidine may be given in doses of 0.2 Gm. (3 grains) three or four times a day.

4. TONIC DOSES.—Digitalis is probably of value in the elderly patient with *myocardial weakness* and mild symptoms of failure, presumably by increasing the water content of the heart muscle. Christian advocates the continuous administration of digitalis in cases of cardiac enlargement, particularly in older people. Many physicians regard digitalis as indicated in *hypertension*, especially when associated with cardiac enlargement. It has been suggested (Cloetta) that digitalis be administered in certain cases of *valvular disease* unaccompanied by signs of cardiac insufficiency.

Erickson and Fahr (1945) placed a group of patients with clinically compensated, but organically diseased, hearts on a maintenance digitalis dosage and felt that the condition of the hearts was improved. Levine (1945) felt that this type of therapy was up to question. He believes that if the heart is not dilated its output may be diminished by digitalis. Until more evidence has been accumulated, however, routine administration of digitalis in unselected cases of chronic valvular disease and other conditions is to be advised against, as it would only lend to the confusion of the problem and delay final solution.

5. THERAPEUTIC TEST.—The effects of digitalis in heart failure are specific, hence, it is a valuable therapeutic test in certain heart conditions. The prompt disappearance of symptoms, after its proper use, suggests heart failure as the cause. The degree of improvement following digitalis therapy indicates the degree of the myocardial damage to a certain extent and is therefore of prognostic value.

TABLE XXII

FUNCTION		DIGITALIS	VAGUS STIMULATION	QUINIDINE
Tonus		Increased	Decreased	Decreased
Contractions		Stronger	Weaker	Weaker
Refractory phase		Longer	Shorter	Longer
Conduction		Stronger but slower	Faster but weaker	Slow and weak
Partial heart block		Exaggerated by long refractory pause	Exaggerated by weak conduction	Probably exaggerated by long refractory pause and poor conduction
Auricular Fibrillation	Aur. rate	May be decreased by lengthened refractory or increased by heightened irritability	Increased by shortened refractory period	Decreased by lengthened refractory period and diminished excitability
	Ventr. rate	Slowed by lengthened refractory period of bundle	Slowed by weak conduction bundle	Slowed by lengthened refractory period and diminished excitability of bundle and muscle

Use in Special Cardiac Lesions.—In various cardiac lesions the indications for the use of digitalis arise only when compensation fails. In mitral *stenosis* lengthening of the auriculoventricular pause may permit better emptying of the auricle. In *aortic insufficiency* digitalization is not contraindicated. In *high blood pressure* digitalis may be of little use, but this condition does not contraindicate its use. In auricular fibrillation with *myocardial infarcts* digitalis generally is harmful (Askey and Neurath, 1945).

The contrasting action of digitalis and quinidine is admirably portrayed in Table XXII (Sollmann, 1948).

Doubtful Indications.—*Myocardial Insufficiency.*—In conditions in which normal rhythm suffers from congestive failure, the use of digitalis may be very beneficial. The exact manner of action is in doubt, but it seems to be effected through the increase in cardiac output due to direct action on the cardiac muscle.

Extrasystoles.—Extrasystoles are signs of hyperexcitability, and since digitalis produces extrasystoles, it would appear that digitalis would be harmful. But clinical results have shown that digitalis may cut off the effect of auricular extrasystoles on the ventricle and even abolish both auricular and ventricular extrasystoles. The use of digitalis to control spontaneous extrasystoles appears at present to have a restricted place.

Paroxysmal Tachycardia.—Although digitalis can produce this condition, nevertheless, in certain cases of supraventricular (nodal or auricular) origin the drug may stop the attack. Carotid sinus pressure may be tried first. Mecholin often in dosage of 20 to 40 mg. (⅓ to ⅔ gr.) may be used effectively in obstinate cases. In a few cases, especially in infants, *digitalis* does, however, have a favorable inhibitory effect (P. D. White, 1941).

Pulsus Alternans.—The presence of this condition does not contraindicate digitalis therapy. Benefit may follow digitalis administration, but great care must be exercised in its administration, as the therapeutic and toxic dose are close in this condition.

Coronary Thrombosis.—Digitalis is thought to have no value in the treatment of coronary thrombosis. By increasing the force of systolic contraction there is the possibility of augmenting the damage already present. On the other hand, digitalis may be of value in relieving the pain of coronary thrombosis by improving circulation.

In cases of *incomplete heart block* in which Adams-Stokes seizures occur, digitalis action may tend to induce attacks by increasing the block; the improvement from digitalis, however, may tend to lessen the attacks. It is therefore apparent that no hard and fast rule regarding its use can be formulated. The possibility of causing Adams-Stokes attacks must be recognized, and against this must be weighed the probability of beneficial muscle action. On the other hand, in complete heart block, real benefit may result from improvement in tonus and by increasing the amplitude of cardiac contraction. Complete heart block constitutes no contraindication to digitalis, but it usually implies an extensive myocardium lesion, and hence great care in digitalis administration is warranted. The optimum dosage must not be exceeded.

Exophthalmic Goiter.—The tachycardia of goiter does not respond to digitalis. It would seem that digitalis is contraindicated in this condition because it would have a tendency to augment the irritation of an already irritated cardiac muscle. Naturally when auricular fibrillation and congestive heart failure are superimposed on the condition, digitalis would be indicated.

Pneumonia.—There is no evidence to substantiate the conception that the mortality rate in lobar pneumonia is reduced by routine digitalization. In fact, there is some evidence to indicate that the mortality rate is increased among those patients receiving digitalis. In an admirable review of the question of the routine employment of digitalis in pneumonia, Treiman's conclusions were that most of the symptoms, such as tachycardia, cyanosis, dyspnea, and cardiac dilatation, which might be classed as circulatory, "are due either to physiological response or to causes other than cardiac," and that "the evidence available at present does not justify the routine use of digitalis in pneumonia."

Diphtheria.—The occurrence of cardiac damage by diphtheria constitutes no indication for digitalis. Moderate amounts of digitalis might even be harmful when superimposed upon the effects of diphtheria toxin upon the heart.

In Valve Defects.—The status of the myocardium and not the valve lesion determines whether digitalis is indicated. Certain valve defects, however, such as aortic lesions, respond with poorer results than do mitral lesions. This may be explained in part by the fact that many aortic lesions are syphilitic in origin and are relatively refractory to digitalis while many of the mitral lesions are rheumatic in origin and are associated with auricular fibrillation.

In Shock.—The tendency to administer drugs in shock should be discouraged, as the mechanism of peripheral circulatory failure is entirely different from that of heart failure. Therapeutic amounts of digitalis have no important vasoconstrictor effect and have little consistent effect on blood pressure. The available evidence seems to indicate that digitalis is harmful, for the systolic discharge of normal hearts is lessened by digitalis, and shock, as we now understand it, implies no cardiac effect.

Routine Administration Before Operation.—Digitalis has been administered as a preoperative routine, insuring its availability in case it were needed. It was hoped that such conditions as tachycardia, abnormal rhythms, shock, and other untoward conditions might then be guarded against. With our present knowledge, however, it appears that the rationale of such usage is erroneous and that, in addition, its use is actually contraindicated. Since simple tachycardia, unassociated with heart failure, cannot be expected to yield to digitalis therapy and since the lowering of circulation rate in cases without heart failure is detrimental, no valid reason is at hand to warrant its use in surgery. In cases of auricular fibrillation or flutter, or congestive heart failure with normal rhythm, digitalis may be part of the necessary treatment to secure the best possible circulatory efficiency before operation.

In Septicemia.—The objections cited in the preceding sections relating especially to the use of digitalis in shock, as a preparation for operation, and in rheumatism apply in general to its use in septicemia and in other toxic states. Such employment of digitalis rests upon the hope rather than upon expectation of benefit.

Digitalis Contraindications.—Apparently there are few, if any, contraindications to the use of digitalis. Gold (1942) made the statement that there are no contraindications to the use of digitalis.

Methods of Digitalis Administration.—There is no fixed method which must be employed in the administration of digitalis; various rigid formulas for digitalization should not be adhered to too closely. Despite the long usage of digitalis it is probably the most misused drug in present-day therapeutics. Many physicians prescribe it on the mere suspicion of the existence of heart disease, regardless of the type of lesion or state of function of the heart. It must be remem-

TABLE XXIII

PREPARATION	SOURCE	INTESTINAL ABSORPTION	DURATION OF EFFECT	AVERAGE DIGITALIZING DOSE		AVERAGE MAINTENANCE DOSE
				ORAL	INTRAVENOUS	
Digitalis	Digitalis purpurea	Irregular	Long	1.5 Gm.		0.1 Gm.
Digitoxin	Digitalis purpurea	Complete	Long	1.2 mg.	1.2 mg.	0.2 mg.
Digoxin	Digitalis lanata	Incomplete	Intermediate	2 to 4 mg.	1 mg.	0.5 mg.
Lanatoside C	Digitalis lanata	Incomplete	Intermediate	8 mg.	1.4 mg.	1 mg.
Ouabain	Strophanthus gratus	Nil	Brief		0.5 mg.	

bered that the intelligent use of digitalis requires a thorough knowledge of the pharmacological action of the drug, a knowledge of when to administer the drug, and how to administer the drug.

Dosage.—The therapeutic dose of digitalis varies widely with different individuals. The advice of Withering still holds: "Let the medicine be continued until it either acts on the kidneys, the stomach, the pulse or the bowels; let it be stopped upon the first appearance of any of these effects."

Maintenance Dose.—A maintenance dose must be given daily in order to prevent elimination of the drug below the therapeutic level. This maintenance dose is approximately 0.1 Gm. (1½ grains) of the standard powder, or 1 cc. (15 minims) of the standard tincture (White). The maintenance dose has to be determined individually on the requirement of the patient.

It must be remembered that the patient should not be subjected to arbitrary dosage in an attempt to force some anticipated result; it is the effect produced that must govern the amount to be administered to produce the original digitalization and the amount necessary to maintain the patient at the proper therapeutic level.

Table XXIII includes the maintenance doses of the various "Digitalis Drugs."

1. ORAL ADMINISTRATION.—Many schemes of digitalization with the leaf, by mouth, are recommended. Probably the one most commonly employed is as follows: Give 4½ grains (0.3 Gm.) three times daily for the first day, and 1½ grains (0.1 Gm.) three times daily thereafter until the optimal therapeutic effect or minor toxic symptoms appear. Thereafter, a dose of from 0.06 to 0.1 Gm. daily as a maintenance dose should suffice.

When there is no urgency, digitalis may be given less rapidly. *Procedure:* Administer 0.2 Gm. daily for about two weeks or until proper drug effect is secured. The dose is decreased to the maintenance dose of 0.06 to 0.1 Gm. daily.

Oral Administration of Purified Glycosides.—Complete digitalization may be secured with a single dose of the glycoside digitoxin which appears to be totally and regularly absorbed (see Table XXIII). *Procedure:* Administer a single dose of 1.2 mg. (six 0.2 mg. tablets) orally. Thereafter a daily administration of 0.2 mg. suffices for maintenance. Digitalization is achieved in a period of six to ten hours. *Remember dosage of this size can be employed only in patients who have not had digitalis for the preceding ten days at least.*

2. INTRAVENOUS ADMINISTRATION.—The sole object of intravenous administration is to save life until administration by mouth is feasible. Many intravenous preparations are now available. Crystalline ouabain, the glycoside obtained from *Strophanthus gratus,* is the drug of choice in America.

Various dosage schedules are used with good results. Most conservative men give only one dose (1/120 grain, 0.5 mg.) of ouabain. No further digitalis is given on the same day, but oral administration of a digitalis preparation in maintenance doses should be begun the next day. Some clinicians (Batterman et al., 1940) give 1/120 grain (0.5 mg.) of ouabain intravenously and 10 grains (0.6 Gm.) of digitalis leaf by mouth (average adult). No further medication is given for twenty-four hours; then the proper maintenance dose is determined and administered.

3. INTRAMUSCULAR ADMINISTRATION.—If vomiting is severe and the intravenous route is contraindicated, digitalis may be given by muscle.

One of the older injectable preparations containing mixtures of glycosides may be preferable to the pure digitalis glycosides, as they are probably less irritant.

4. RECTAL ADMINISTRATION.—This route may be used when the oral route is not feasible. The absorption is at least as rapid as with the oral route, and the dosage is probably the same. One may employ 4 cc. of the tincture in six ounces of saline every four to six hours. The drug has also proved effective in suppositories of about 0.2 Gm. (3 grains) strength.

Dosage for Children: For a child weighing 50 pounds, Taussig (1947)* at Johns Hopkins Hospital gives the following: 1½ grains (0.1 Gm.) as test dose; two hours later, 3 grains (0.2 Gm.); eight hours later, 3 grains again; and eight hours thereafter, 1½ grains. If not digitalized at end of twentieth hour, continue 1½ grain doses every six hours for one or two more doses provided there are no signs of toxicity, then place the child on maintenance dosage.

Digitalis Preparations

Choice of Preparation.—No satisfactory answer is yet available as to the best digitalis preparation in the therapy of heart disease. Sollmann (1948) says: "The powdered standardized leaf (Digitalis Pulverata, U.S.P.), dispensed in tablets, is perhaps the best form of oral digitalis medication." The following statement by Gold (1948) favors the purified glycoside: "The use of digitoxin has greatly simplified the problem of digitalization. I advocate it as the material of choice for routine digitalization and maintenance."

The practitioner would probably place the treatment of heart disease on a higher plane if he would confine his prescribing to the following three preparations: *digitalis leaf, digitoxin,* and *ouabain.* Other preparations may be equally as useful and some may even have special advantages, but in the present state of our knowledge it seems wise to gain a thorough experience with these outstanding preparations and not become confused by the multiplicity of proprietary drugs now available. It is probably true that the official leaf orally, and ouabain intravenously, will accomplish everything that can be accomplished in heart disease by drugs of this group.

The Digitalis Unit.—"The International Unit," which is official in the U.S.P. and B.P., corresponds to 0.1 Gm. of the U.S.P. standard reference powder. Since different samples of crude drugs vary so widely in potency, it is necessary to adjust their strength by bio-assay to uniform potency by comparison with an international reference standard sample.

Bio-assay.—The official method of bio-assay employs etherized cats as the test animal. The powdered drug (and the standard) are macerated in an alcoholic medium. The solution is infused in the femoral veins into lightly etherized cats in fractional doses five minutes apart until cardiac arrest occurs after thirteen to nineteen doses. At least, a dozen cats are required for a complete bio-assay. (Details given in the U.S.P.)

The main criticisms of this method are that it is a measure of the toxicity of the preparations, which is not necessarily related to their therapeutic effect. Second, it employs intravenous injection, it entirely disregards absorbability, and therefore is misleading for oral dosage of different digitalis principles. Although the cat assay of U.S.P. disregards absorption, its potency agrees fairly well with the oral clinical assay but not for isolated principles. (Catell and Gold, 1944.)

The method of assay on human beings as devised by Catell and Gold at Cornell is probably the best method available, but the findings have not been completely confirmed and this method requires extensive clinical facilities to provide a uniform group of patients.

The purified glycosides, lanatoside C, obtained from *Digitalis lanata;* digoxin, also obtained from *D. lanata;* and digitoxin, obtained from *D. purpurea,* being apparently chemical entities, can be identified by chemical means. Preparations of these compounds, however, must be standardized biologically against their respective U.S.P. reference standards since the amounts present in the accepted dosage forms are too small for chemical or physical identification. The U.S.P. Digitoxin Reference Standard must be used to assay digitoxin biologically.

Deterioration.—Powdered digitalis properly prepared appears to suffer little loss of potency with age. Haag and Hatcher found that powdered digitalis leaves are most stable, showing no deterioration after a period of sixteen years when stored in dry containers, and the official tincture remained unchanged for several years. The infusion (N.F.) is liable to deteriorate in strength, especially if not kept in sterile containers. Aqueous solutions of strophanthin and ouabain, when placed in soft glass ampules, may deteriorate, but when put up in hard glass ampules or with buffer solutions, no change occurs over long periods of time.

U.S.P. Preparations of Digitalis.—The powdered standardized leaf (Powdered Digitalis, U.S.P.), dispensed in tablets, is perhaps the best form of digitalis for oral therapy. The U.S.P. Digitalis Tincture may have some advantage when the dose is being adjusted. It does not deteriorate materially within a year. The injectable U.S.P. preparations are solutions of the partly purified water-soluble principles. They have no advantage over ordinary digitalis preparations for oral use. They have little advantage over ouabain or strophanthin for parenteral use, other than being more lasting.

Preparations of isolated digitalis principles found in the U.S.P. include Digitoxin, Digoxin and Lanatoside C. *Digitoxin* is subject to the same precautions as is digitalis, but has the advantage that it is almost completely absorbed and thus is nearly as effective by mouth as by vein. *Digoxin* shares the latter's advantage over digitalis in being more completely absorbed by mouth. It is probably the most cumulative of the lanatosides, which are generally superior in this respect to *Digitalis purpurea* because of their rapid absorption and elimination. *Lanatoside C* is essentially the same as digoxin that represents the active residue of this lanatoside. It is likewise absorbed more completely on oral administration than the purpurea glycosides.

Digitoxin and other purified preparations are satisfactory now for routine use and have the advantage over the leaf itself in that one may rely on the preparation quantitatively by weight without need of standardization except on each individual patient.

It would appear that we are going through a transition period from the use of the digitalis leaf to the use of pure glycosides. The transition has been very slow, however, for Nativelle, as long as one hundred years ago, produced the first purified glycoside (digitaline) which is our digitoxin of today.

Proprietary Digitalis Preparations.—Several digitalis preparations have been introduced in therapeutic use with the claim that they are composed either of pure principles, or of purified extracts of digitalis, and that they are devoid of certain disadvantages possessed by the U.S.P. preparations. Without question, some of these preparations are of first-class quality, but there is no proof that any of these proprietary

preparations are more effective in the treatment of the majority of cases of cardiac disease than are digitalis and its galenicals. (See N.N.R. for details.)

PREPARATIONS

Digitalis, *Digitalis,* U.S.P. (Foxglove, Digitalis folium P.I.). The dried leaves. Potency: 0.1 Gm. is equivalent to not less than 1 U.S.P. Digitalis Unit (international unit).

Powdered Digitalis, *Digitalis Pulverata,* U.S.P. Potency: 0.1 Gm. equivalent to 1 U.S.P. Digitalis Unit. *Dosage:* 0.1 Gm. (1½ grains).

Digitalis Capsules, *Capsulae Digitalis,* U.S.P. The usual sizes contain 50 mg. and 100 mg.

Digitalis Infusion, *Infusum Digitalis,* N.F. Powdered Digitalis, U.S.P. (1.5 per cent), alcohol (10 per cent), cinnamon spirit and distilled water, freshly prepared. This is an effective form of digitalis but has no advantage over the tincture. *Dosage:* 6 cc. (1½ fluidrams).

Digitalis Injection, *Injectio Digitalis,* U.S.P. A sterile solution of one or more of the glycosides or therapeutically desirable and cardioactive constituents of digitalis in water for injection. *Dosage:* Intravenous, 1 U.S.P. Digitalis Unit.

Digitalis Tablets, *Tabellae Digitalis,* U.S.P. The usual size contains 50 mg. and 100 mg.

Digitalis Tincture, *Tinctura Digitalis,* U.S.P. (Tinctura Digitalis P.I.). Digitalis (10 per cent) in alcohol and water. Potency: 1 cc. is equivalent to 1 U.S.P. Digitalis Unit. Alcohol content about 70 per cent. *Dosage:* 1 cc. (15 minims).

Digitoxin, *Digitoxinum,* U.S.P. Either pure digitoxin ($C_{41}H_{64}O_{13}$) or a mixture of cardioactive glycosides obtained from *Digitalis purpurea* Linné and consisting chiefly of digitoxin. Its potency, assayed biologically, corresponds to the potency of an equal weight of U.S.P. Digotoxin Reference Standard. *Dosage:* Oral, 0.1 mg. (1/600 grain). Intravenous, to be determined by the physician according to the needs of the patient (U.S.P.).

Digitoxin Injection, *Injectio Digitoxini,* U.S.P. A sterile solution of digitoxin in 40 to 50 per cent alcohol solution, with or without glycerin. *Dosage:* Intravenous to be determined by the physician according to the needs of the patient (U.S.P.), usually available in ampuls containing 0.1 mg. in 1 cc.

Digitoxin Tablets, *Tabellae Digitoxini,* U.S.P. *Dosage:* 0.1 mg. of digitoxin (U.S.P.), usually available in tablets of 0.1 and 0.2 mg.

Digoxin, *Digoxinum,* U.S.P. A glycoside obtained from the leaves of *Digitalis lanata,* Ehrh, or Digitalis orientalis. The potency, assayed biologically, corresponds to the potency of an equal weight of U.S.P. Digoxin Reference Standard. *Dosage:* Oral, 0.5 mg. (U.S.P.). The initial oral digitalization dosage is about 1 to 1.5 mg., followed by 0.25 mg. at six-hour intervals to obtain the desired effects; the daily maintenance dose is 0.25 to 0.5 mg.

Digoxin Injection, *Injectio Digoxini,* U.S.P. Sterile solution of digoxin in 70 per cent alcohol. It contains the labeled amount of digoxin. *Dosage:* The intravenous digitalization dosage is about 1.5 mg. usually divided into two doses; the maintenance dose is 0.25 mg. to 0.5 mg. daily.

Digoxin Tablets, *Tabellae Digoxini,* U.S.P. *Dosage:* 0.5 mg. of digoxin (U.S.P.), usually available in tablets containing 0.25 mg.

Lanatoside C, *Lanatosidum C*, U.S.P.—$C_{49}H_{76}O_{20}$—A glycoside obtained from the leaves of *Digitalis lanata* Ehrh. The potency of lanatoside C, assayed biologically, corresponds to the potency of an equal weight of U.S.P. Lanatoside C Reference Standard. *Caution: Lanatoside C is extremely poisonous. Dosage:* Oral, 0.5 mg. Parenteral, to be determined by the physician according to the needs of the patient.

Lanatoside C Injection, *Injectio Lanatosidi C*, U.S.P. A sterile solution of lanatoside C in 70 per cent alcohol, to which glycerin may be added. *Dosage:* To be determined by the physician according to the needs of the patient. The total intravenous or intramuscular digitalization dose is about 1.6 mg., usually divided into two or four doses given at twelve-hour intervals.

Lanatoside C Tablets, *Tabellae Lanatosidi C*, U.S.P. *Dosage:* Oral, 0.5 mg. of lanatoside C.

Other Members of the Digitalis Group

Ouabain (crystallized strophanthin, g-strophanthin). Ouabain is a glycoside ($C_{29}H_{44}O_{12}.8H_2O$) obtained from *Strophanthus gratus.*

Action and Uses.—The pharmacological action of crystallized ouabain is probably qualitatively identical with that of the official strophanthin, but the crystallized ouabain is uniform while K strophanthin is amorphous and varies in composition from lot to lot. Ouabain, therefore is to be preferred. Ouabain is absorbed so slowly and irregularly from the alimentary tract that oral administration is contraindicated.

For patients extremely ill, in whom the digitalis effect is indicated, intravenous medication of ouabain may be indicated. *Dosage:* 0.5 mg. ($\frac{1}{120}$ grain) is indicated for intravenous or intramuscular use. This dose should not be repeated within twenty-four hours. Before administration dissolve in 4,000 to 8,000 parts of physiological saline. If administration is to be repeated within twenty-four hours, a smaller volume of saline is recommended. Ouabain solutions deteriorate rapidly, especially in soft glass containers, therefore use only recently prepared solutions.

PREPARATIONS

Ouabain, *Ouabainum*, U.S.P. (G-Strophanthin). A nonnitrogenous glycoside $C_{29}H_{44}O_{12}.8H_2O$. *Dosage:* Intravenous, 0.25 mg. U.S.P.

Ouabain Injection, *Injectio Ouabaini*, U.S.P. A sterile solution of ouabain in water for injection. The usual sizes contain 0.25 mg. and 0.5 mg. in 1 cc.

Strophanthin.—Strophanthin is a glucoside or mixture of glucosides obtained from seeds (0.45 to 1%) of *Strophanthus Kombé* or of *Strophanthus hispidus.* The glucoside is a white powder, very soluble in water, which makes it available for intravenous use.

It is generally accepted that pharmacological properties of strophanthin and digitalis are practically identical, except that strophanthin acts more promptly and is eliminated with greater speed (Fraenkel, 1933). The more rapid elimination or destruction of strophanthin accounts for its noncumulative action after repeated injections. The absorption of strophanthin is so uncertain that oral administration is not advisable (Hatcher and Bodey, 1909). Oral use is also attended usually by diarrhea. Difference of opinion exists concerning the *toxicity* of strophanthin. If properly administered to suitable patients, the drug probably has its place in cardiac therapy. Grunbaum (1931) gave over 10,000 injections of strophanthin without observing a single death.

The use of strophanthin is usually confined to emergencies in which it is employed intravenously in full dose of 0.5 mg. (1/120 gr.). Its effect on the heart may be evidenced in a few minutes to one hour. If the desired effect is not obtained in two hours the dose of 0.1 mg. may be given every half hour up to a total dose of 1 mg.

PREPARATION

Strophanthin, *Strophanthinum*, N.F. A glycoside or mixture of glycosides obtained from *Strophanthus* having a potency equal to 40 to 60 per cent of standard ouabain, U.S.P. *Dosage:* Intravenous, 0.5 mg.

Squill.—Squill is the cut, dried inner scales of the bulb of the white variety of *Urginea maritima*. This drug, also a member of the digitalis group, has been used since before the days of Hippocrates, but in recent times it has been little employed.

Squill produces the same effects as digitalis, experimentally and clinically. It may be used as an expectorant, diuretic, and emetic, but better drugs are now available for these purposes. When employed as an expectorant, the syrup may be prescribed. It is usually associated with other agents when prescribed for either of these uses.

SCILLAREN-*B*, N.N.R.—Glucosidum e scilla solubile.—This is the amorphous component of the natural mixture of the glucosides occurring in squill, *Urginea maritima*. *Dosage:* Scillaren-B is for intravenous administration when immediate action is indicated. Administer not more than 0.5 mg. (1/130 grain) of scillaren-B intravenously within twenty-four hours.

SCILLAREN, N.N.R.—Glucosidum e scilla totum.—This is a mixture of the natural glucosides, scillaren-A and scillaren-B, occurring in fresh *Urginea maritima* in the same proportion as found in the fresh drug, namely scillaren-A to scillaren-B (2:1). The cardiac action of scillaren is similar to that of digitalis, but this action is apparently less persistent. *Dosage:* Administer 1.6 mg. (1/40 grain) orally three to four times daily until compensation is established or until minor toxic symptoms appear. After compensation is established administer 0.8 mg. (1/80 grain) from two to four times daily.

DRUGS ACTING MAINLY AS CARDIAC DEPRESSANTS

The cardiac muscle is, as a general rule, more sensitive to the action of poisonous drugs than any other tissue in the body except the central nervous system. Consequently, a large number of drugs act as cardiac depressants, but few drugs are suitable for use therapeutically for cardiac depressant action. The anesthetics and hypnotics, especially those containing chlorine, act as cardiac depressants. This effect is a side reaction of these drugs, but this action must be taken into consideration when administering them. Quinidine is used in medicine for its cardiac depressant action.

Quinidine

Quinidine, $C_{20}H_{24}O_2N_2 + 2H_2O$, one of the cinchona alkaloids, acts as a cardiac depressant. It is a dextro-isomer of quinine. The drug is a white, odorless powder or crystals, with an intensely bitter taste. Quinidine sulfate is soluble in water (1:90) and in alcohol (1:10). Wenckebach (1914) noted, during the treatment of malaria, that patients who had auricular fibrillation were greatly benefited by the quinine. Upon further investigation it was found that quinidine excelled quinine in its beneficial effect on this heart disorder.

However, the enthusiasm for quinidine soon waned because of the number of unexpected deaths attributed to it, and the pendulum swung back to nearly complete abandonment of the drug. Its recent use has increased because of the growing realization of its effectiveness in certain cardiac conditions.

Pharmacological Action.—It is now established that quinidine prolongs the refractory phase of the heart and the electrical systole of the ventricles. It prolongs conduction in the ventricles, in the auriculoventricular junction, and, to a certain extent, in the auricles. It depresses the sinus node and thus slows the heart rate. It decreases excitability of the myocardium. It paralyzes the vagus nerve, which tends to neutralize to some degree its direct effects on the sinus node and auricles.

In excess, quinidine tends to depress the myocardium, and may lead to respiratory disturbances and even respiratory paralysis. In large doses, by reason of its action on smooth muscle, it may cause a fall in blood pressure.

Quinidine is rapidly absorbed and excreted. Orally, the maximum effect is obtained in from two to four hours. Minimal residual effects persist for six to eight hours and urinary excretion is complete in twelve to twenty-four hours. Therefore, repeated oral doses given more than six hours apart are not cumulative. When administered intravenously or intramuscularly, the maximum effect occurs in one-half to one and one-half hours.

Digitalis Action vs. Quinidine Action.—

1. Digitalis increases irritability of the heart muscle, while quinidine lessens it.
2. Quinidine apparently cures fibrillation by depressing or stopping the origin of impulses in the auricle, while digitalis prevents the passage of impulses to the ventricle.
3. Both reduce conductivity through the bundle, but digitalis to a greater degree.

Quinidine has no true pharmacologic antidote. The drug of choice to counteract respiratory depression is caffeine with sodium benzoate. Metrazol, amphetamine, and nikethamide are effective.

Toxicology.—Although similar to quinine toxicologically, quinidine may produce other symptoms than those evidenced by quinine. Therapeutic doses rarely cause toxic symptoms, but occasionally there appears a feeling of fullness of the head, headache, dizziness, tinnitus, visual disturbances, skin eruptions, and gastric disturbances. Rarely, severe gastrointestinal symptoms may contraindicate oral administration. Recently an injectable form of quinidine, quinidine hydrochloride with urea and antipyrine, has been described which is reported to produce more prompt effects than oral quinidine and to have also a longer duration of action. Intravenous injection of quinidine, however, is dangerous and rarely justified. There seems to be a distinct idiosyncrasy to it in susceptible persons; therefore a small preliminary test dose is always advisable. The fatalities due to its administration are usually due to ventricular fibrillation, respiratory paralysis, liberation of emboli due to action on the heart, and collapse accompaned by convulsions. The **fatal dose** varies widely. As much as 15 grains, four times daily, have been given without the production of toxic symptoms.

Treatment **of poisoning consists of gastrointestinal lavage, emesis, and general supportive measures. Caffeine is the antidote for respiratory**

depression. Inhalation of amyl nitrite and retrobulbar injection of 0.25 mg. of atropine sulfate are indicated for the prevention of optical injuries.

Therapeutic Uses.—The indications for quinidine therapy as summarized in the words of the National Research Council (J. A. M. A. 124: 239, 1944) are as follows:

1. Ventricular tachycardia diagnosed electrocardiographically.
2. Congestive heart failure that appears definitely to have been precipitated by the sudden onset of auricular fibrillation (if not adequately controlled by digitalis).
3. Persistent premature ventricular contractions in patients who have had acute coronary artery occlusion.

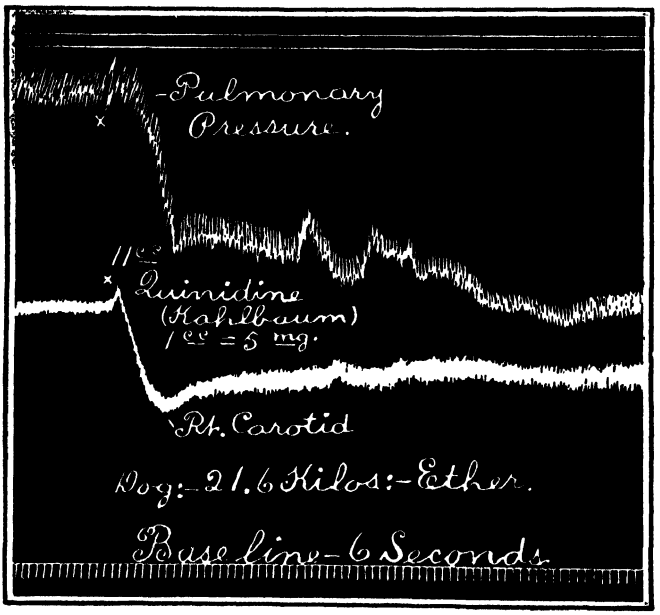


Fig. 23.—Pulmonary and carotid blood pressure showing the action of quinidine. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

4. Chronic heart disease associated with paroxysmal auricular fibrillation, paroxysmal auricular tachycardia, or auricular flutter.
5. A history of systemic embolization in a case of paroxysmal or established auricular fibrillation.

One of the more recent uses of quinidine is its employment to suppress premature systoles. In normal subjects treatment is unnecessary unless symptoms become severe. Quinidine may be used when digitalis causes premature systoles. It may also be used in patients with mitral stenosis complicated by frequent auricular premature systoles in order to prevent or delay the onset of auricular fibrillation (Katz, 1948).

Contraindications.—According to Katz, the only absolute contraindication to the use of quinidine is idiosyncrasy or sensitivity to the

drug. This is manifested by respiratory or circulatory collapse by cinchonism. Most of the contraindications are based on its primary depressant action on the heart. The depressant action on the heart is most apt to appear in conjestive heart failure and cardiac enlargement. It is contraindicated in the presence of heart block.

Administration.—Quinidine may be administered orally, intramuscularly, or by vein. The oral route is the method of choice. A test dose for sensitivity of 0.2 Gm. should be given. For therapeutic effect, 0.4 Gm. should be given every two hours until the end of arrhythmia or until five doses have been given. This may be repeated for two or three days, the dose being increased each day by 0.2 Gm. If toxic symptoms appear, the drug should be stopped.

When the arrhythmia is stopped, 0.2 Gm. of quinidine should be given three times a day for a week. If the arrhythmia is recurrent, maintenance therapy of 0.2 Gm. two or three times a day should be given.

Intramuscular therapy may be used to secure more rapid action (one-half to one and one-half hours) or when oral therapy is contraindicated. Quinidine sulfate or quinidine hydrochloride may be used.

The intravenous route is dangerous and is rarely necessary.

Paroxysmal Auricular Tachycardia.—Paroxysms of tachycardia of auricular origin start and finish abruptly. The rate varies from 120 to 220 beats per minute. The attacks ordinarily stop in a few hours, but therapy may hasten return to normal rhythm.

Quinidine to depress the heart muscle is a useful measure. Give in a dose of 0.1 Gm., orally, to test drug sensitivity. Continue therapy in four hours if no signs of sensitivity appear. The dose is then 0.2 to 0.4 Gm. every four hours. Quinidine is probably safer and more desirable than methacholine.

In an emergency, other measures having failed, give quinidine sulfate intravenously. Give slowly 0.2 to 0.4 Gm. dissolved in 500 cc. of physiological saline solution. Stop injection when rhythm has reverted to normal.

Paroxysmal Ventricular Tachycardia.—This condition is usually associated with grave myocardial disease. If the paroxysm is prolonged, or if brief paroxysms are recurring frequently, quinidine should be given at once. Treatment consists of the administration of quinidine as described for paroxysmal auricular tachycardia. Digitalis is probably contraindicated.

Auricular Fibrillation.—Striking results follow the use of digitalis in the treatment of this condition. Auricular fibrillation constitutes a half of all cardiac irregularities (Lewis) and, according to Mackenzie, two-thirds of all serious cardiac failures.

If the cardiac damage is slight, and especially in the fibrillation persisting after thyroidectomy, an attempt to restore a regular beat with quinidine sulfate is indicated.

Procedure: Administer digitalis to bring ventricular rate to about 70 per minute. It should be continued throughout trial with quinidine. Next, give a single dose of 0.2 Gm. of quinidine as a test dose. If no signs of toxicity appear in twenty-four hours, then administer quinidine every four hours day and night to maintain effective concentration of the drug. It is usually started with 0.2 Gm. every four hours and increased to 0.4 Gm. every four hours on the third day. Maintain for one week unless reversion to normal rhythm has not occurred. If treatment fails, repeat after a rest of one week. A maintenance dose of 0.2 to 0.4 Gm., one to four times daily, may be necessary.

Auricular and Ventricular Extrasystoles.—These arrhythmias may respond to quinidine therapy. It may be useful in the cases that are

attended by discomfort. In young patients, with no evidence of organic disease, the continued use of quinidine should not be resorted to. Wenckeback, the authority on arrhythmias, recommends 0.3 to 0.4 gram (5 to 6 grains) of quinidine daily, plus 2 or 3 mg. ($\frac{1}{80}$ to $\frac{1}{20}$ grain) of strychnine for a ten-day period.

Auricular Flutter.—Quinidine is useful in the treatment of auricular flutter, especially in those cases in which digitalis causes a change in auricular fibrillation but in which the further step to normality does not follow.

Administration and Dosage: The intravenous use of the drug is rarely indicated except in special cases. That the drug is an effective agent is indicated by the fact that the heart slows gradually. The maintenance dose is about 0.25 gram per day. If no benefit follows the first seven days' use, quinidine is usually considered unsuccessful and the treatment stopped.

The initial dose is usually 0.2 gram (3 grains). If no toxic symptoms appear (nausea, vomiting, headache, palpitation, etc.) administer 0.2 to 0.4 gram (3 to 6 grains) three to four times a day. The change to normal rhythm may occur in from one to three days.

Malaria.—Quinidine is also employed in the treatment of malaria, especially in patients who have an idiosyncrasy for quinine. Sanders (1936), after using the drug in 1,349 cases, thought it superior to quinine in controlling the acute attack and in preventing relapses. In this series it did not prove to be a dangerous heart depressant.

Preparations

Quinidine Sulfate, *Quinidinae Sulfas,* U.S.P. *Dosage:* Caution. 0.2 Gm. (3 grains) four times a day. *Quinidinae Sulphas,* B.P. *Dosage:* 0.2-0.6 Gm. (3-10 gr.).

Quinidine Sulfate Tablets, *Tabellae Quinidinae Sulfatis,* U.S.P. The usual sizes contain 0.1 Gm., 0.2 Gm., and 0.3 Gm.

Nitrites

The medicinal "nitrite group" comprises salts and esters of nitrous acid and certain organic nitrates, all of which are reduced to nitrites in the body. The important members of this group are:

Inorganic	Sodium Nitrite	$NaNO_2$
Organic	Amyl Nitrite	$C_5H_{11}NO_2$
	Ethyl Nitrite	$C_2H_5NO_2$
	Glyceryl Trinitrate	$C_3H_5(NO_3)_3$
	Erythrityl Tetranitrate	$C_4H_6(NO_3)_4$
	Mannitol Hexanitrate	$C_6H_8(NO_3)_6$

Pharmacological Action.—The action of the "nitrite group" depends on the nitrite radical (-O-N-O), which acts directly to inhibit the tone of all smooth muscle. It is responsible for their effect as vasodilators.

Absorption and Excretion.—The relative rapidity of absorption of the nitrites is shown in Table XXIV—Blood Pressure Results in Hypertensive Person.

Amyl nitrite is very volatile and is readily absorbed from the lungs. It is administered only by inhalation. When swallowed amyl nitrite is relatively inactive because the gastric juice acts on it to liberate nitrous acid which is immediately decomposed. *Nitroglycerin* is more

readily absorbed when placed under the tongue (sublingual route) than by the intestinal route. It is also absorbed through the skin. *Sodium nitrite* is absorbed from the intestinal tract, large doses may cause gastric irritation, nausea, and vomiting. Sodium nitrite should be administered only by the oral route.

About 60 to 70 per cent of absorbed nitrite is destroyed and its fate is unknown. No cumulative action is evident.

Action on Circulation.—The chief action of nitrites is on circulation, and chiefly on the muscular tissue in the vessel walls. The action is apparently not on the vasomotor centers because the pulmonary arteries, which are not believed to possess vasomotor nerves, are dilated by nitrites. The vessels of the splanchnic area are the most strongly affected by nitrites, but a powerful action is exerted in the arteries of the brain, lungs, heart, and limbs, and superficially in the neck and head.

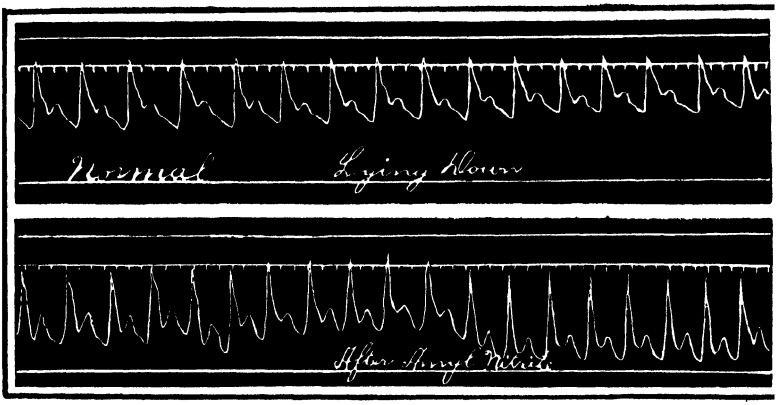


Fig. 24.—Tracing made with Dudgeon's sphygmograph showing the normal pulse record and a pulse record affected by inhaling amyl nitrite. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

The pulse is accelerated and becomes somewhat irregular due to the fall in blood pressure (Fig. 24). This condition results in anemia of the brain, which in turn depresses the tone of the inhibitory cardiac center, causing excitation of the accelerator apparatus. The

TABLE XXIV

BLOOD PRESSURE RESULTS IN HYPERTENSIVE PERSON
(Full therapeutic doses and usual routes of administration)

DRUG	ONSET OF ACTION MIN.	MAXIMUM EFFECT MIN.	SYSTOLE FALL MM. HG	TIME OF RECOVERY MIN.
Amyl Nitrite	½- 1	2- 3	15-25	4- 8
Nitroglycerin	1- 2	5-10	15-30	25- 40
Sodium Nitrite	5-20	25-40	25-40	60-150
Erythrityl Tetranitrate	15-30	30-50	30-40	180-300
Mannitol Hexanitrate	15-30	60-120	30-40	240-360

coronary arteries of the heart are dilated, resulting in improved coronary acceleration. This explains the use of nitrites in the treatment of angina pectoris. Large doses of amyl nitrite slow and weaken the contractions of the heart by direct depressant action on the cardiac muscle.

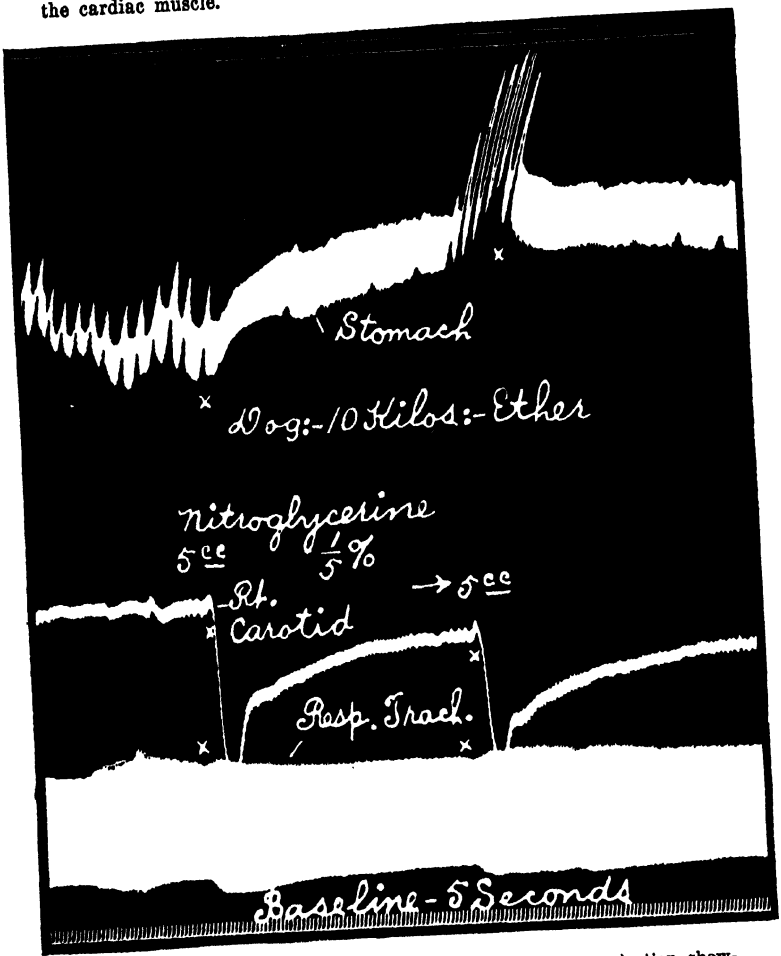


Fig. 25.—Stomach contractions, blood pressure, and respiration showing the action of nitroglycerin (two injections). Note the inhibition of spastic griping in the stomach at each injection. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

Action on Blood.—Large doses of nitrites produce methemoglobin, which may result in cyanosis and asphyxia. Since the blood corpuscles are not destroyed there is recovery. The blood assumes a dark color due to methemoglobin formation. The formation of this compound

is not a specific reaction with nitrites but is the same action as would be caused by any reducing body.

Action on Muscles.—Nitrites depress the involuntary muscle tissue in bronchial tubes to such a degree as to be of value in bronchial asthma. This group of drugs seems to possess a muscle-relaxing effect in spasm of the bile duct or ureter. Nitrites tend to depress smooth muscle of the bowel (Fig. 25).

Effect on Temperature.—The dilatation of cutaneous vessels increases the surface temperature and causes loss of body temperature. In fever there is a marked fall in temperature. Large doses of nitrites lower the normal temperature by depressing circulation.

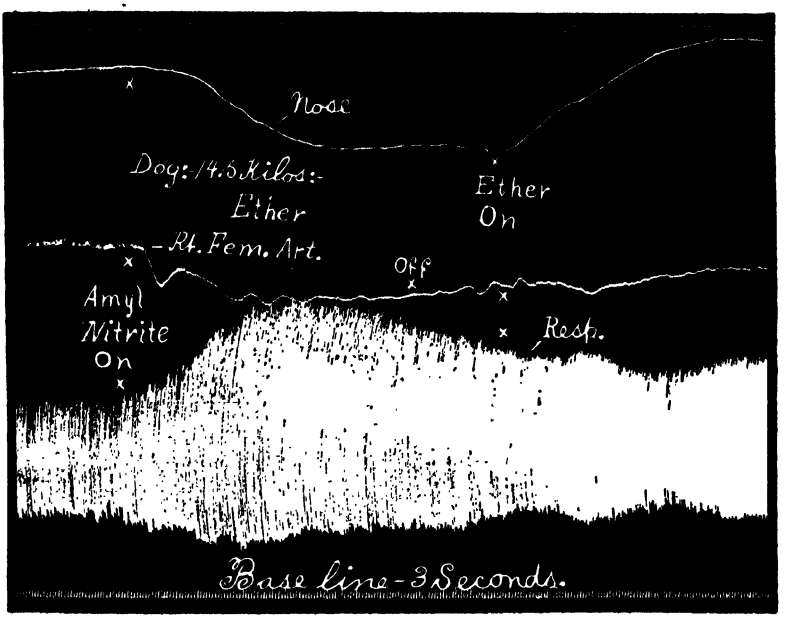


Fig. 26.—Nasal volume, blood pressure (right femoral artery), and respiration showing the action of amyl nitrite and ether (strong vapor at "On"). (From Jackson: *Experimental Pharmacology and Materia Medica.*)

Action on Respiration.—Respiration is accelerated and rendered deeper by nitrites (Fig. 26). The acceleration is the result of a fall in blood pressure which decreases the supply of blood to the brain, thus arousing the respiratory center. The bronchial muscles are relaxed by amyl nitrite and this action affords relief in asthma. This explains the old remedy for asthma, that of burning saltpeter and inhaling the nitrite fumes.

Action on Nervous System.—No direct action on the nervous system is exerted by nitrites, but the marked vasodilation in the cerebral vessels, in conjunction with the fall in blood pressure, may cause headache, dizziness, faintness, blurring of vision, and even convulsions. Amyl nitrite may cause, through stimulation of the nasal mucous

membrane, a temporary rise in blood pressure and inhibitory slowing of the heart.

Effect on Intraocular Tension.—Intraocular tension is raised by amyl nitrite; it must, therefore, be used with caution in glaucoma. The retinal vessels are dilated following its administration.

Effect on Kidneys.—The kidneys are little affected by therapeutic doses, but large doses of nitrites may cause a decrease of urine excretion and even anuria. The renal effects are inconstant and depend, no doubt, on whether the arteries and arterioles are dilated or not.

Toxicology.—The face becomes flushed after taking a few drops of amyl nitrite, and there is a sensation of fullness and throbbing in the head. After toxic doses, there are likely to occur, in addition, such effects as cardiac palpitation with rapid full pulse, markedly flushed face, throbbing head, and rapid respiration. Vomiting and diarrhea are possible symptoms. Mental confusion and muscular weakness may follow. The heart action becomes slow, the respiration shallow and frequently irregular, and cyanosis appears. Amyl nitrite rarely causes death in man.

Some persons respond markedly to small doses of nitrites, while others are unusually tolerant to their action. Severe headaches are most common with the use of nitroglycerin and erythrol tetranitrate.

Excessive doses of any of the nitrites convert hemoglobin to *methemoglobin.* If methemoglobinemia is sufficiently great, cyanosis and functional anemia result. Severe poisoning and even death may follow the use of bismuth subnitrate in the treatment of diarrhea due to nitrite-induced methemoglobinemia.

TREATMENT.—If the drug has been taken orally, evacuate the stomach by stomach tube or an emetic. Give a gastric lavage with 500 cc. (1 pint) of 1:1,000 solution of potassium permanganate. For persistent cyanosis 50 cc. (1⅔ fluid ounces) of 1 per cent in 1.8 per cent sodium sulfate may be given intravenously. Administer strychnine or digitalis. Use cold applications on the head. Give artificial respiration if the occasion demands it. The head-low position to aid return of venous blood to the heart is often useful. If shock is severe, shock therapy is indicated.

HABITUATION.—Habituation may occur from the frequent use of nitroglycerin. The dosage must be increased to get response. Suspension of use of the drug or alternating to another "nitrite" compound may be resorted to. Tolerance is not acquired with sodium nitrite or erythrol tetranitrate.

Therapeutic Uses.—Nitrites are used because of their marked effect in dilating the peripheral vessels and lowering blood pressure. They have been tried for all diseases in which the symptoms indicate vascular spasm, but due to the rather transient action of these drugs, their practical value is limited.

Angina Pectoris.—In cases of spasm of the coronary arteries amyl nitrite (1 to 3 drops) gives prompt relief. Thin glass ampules "pearls" may be crushed and the fumes inhaled, or amyl nitrite may be administered by mouth or by injection. During an attack of angina pectoris amyl nitrite gives relief; an attack may be warded off by administering sodium nitrite or nitroglycerin every four to five hours. In general, in occasional attacks use amyl nitrite, but if recurrent attacks are common, sodium nitrite or nitroglycerin should be taken every four to six hours, on the days which experience has taught the patient the attacks will likely occur.

Nitroglycerin is more dependable than amyl nitrite. It may be prescribed as 0.0006 gram (1/100 grain) hypodermic tablets. They are not volatile, do not deteriorate rapidly, and are less expensive than amyl nitrite.

Chronic Hypertension.—Nitrites have no permanent influence on this condition and should not be administered routinely. Of the nitrite group, erythrityl tetranitrate is probably the least harmful. Give in doses of 30 to 60 mg. every four hours.

Bronchial Asthma.—This respiratory condition may be treated by burning potassium nitrate, generally in combination with belladonna, to dilate the constricted bronchi, through its conversion from a nitrate to a nitrite. A few breaths of amyl nitrite may be of value early in an attack.

Pylorospasm.—Amyl nitrite, inhaled as "pearls" or spirits of glyceryl trinitrate (nitroglycerin), 3 drops on the tongue and increasing the dose by 1 drop every two minutes, is indicated for treatment of this condition. Sodium nitrite, 0.06 gram (1 grain) three or four times a day, may be administered.

Nervous Disorders Characterized by Muscular Spasm.—In *epilepsy,* inhalation of amyl nitrite during the aura will tend to ward off the imminent paroxysm, and in *hysterical seizures* the attacks may be shortened by repeated inhalations of this drug. In *tetanus* a few drops of amyl nitrite may relieve severe paroxysms. In obstinate *hiccup* amyl nitrite may prove effective in relieving the condition.

Localized Spasms of Vessels.—Nitrites have been used to relax peripheral arteriole spasm, such as found in Raynaud's disease and in erythromelalgia. The nitrites may be administered in gradually increasing doses.

Miscellaneous.—Amyl nitrite has been used to assist the heart in ether and chloroform anesthesia; to overcome chloroform collapse; in seasickness; and as a diaphoretic in fevers and colds.

PREPARATIONS

Amyl Nitrite, *Amylis Nitris,* U.S.P., B.P. *Dosage:* 0.2 cc. (3 minims) by inhalation.

Erythrityl Tetranitrate Tablets, *Tabellae Erythritylis Tetranitratis,* U.S.P. *Dosage:* 30 mg. (½ grain).

Sodium Nitrite, *Sodii Nitris,* U.S.P., B.P. *Dosage:* 0.06 Gm. (1 grain).

Sodium Nitrite Tablets, *Tabellae Sodii Nitritis,* U.S.P. Usual sizes contain 30 mg. and 60 mg.

Ethyl Nitrite Spirit, *Spiritus Aethylis Nitritis,* N.F. (Spirit of Nitrous Ether, Sweet Spirit of Nitre). Ethyl nitrite (about 4%) in alcohol. Absolute alcohol content about 90 per cent. *Dosage:* 2 cc. (30 minims). *Spiritus Aetheris Nitrosi,* B.P. *Dosage:* 1-4 cc.

Glyceryl Trinitrate Spirit, *Spiritus Glycerylis Trinitratis,* N.F. (Nitroglycerin Spirit). Glyceryl trinitrate (1%) in alcohol. CAUTION.—Great care must be exercised in dispensing, handling, packing, transporting, and storing this spirit, since a dangerous explosion may result if any considerable quantity of it is spilled, and the alcohol wholly or partially lost by evaporation. If through accident it is spilled, a solution of potassium or sodium hydroxide must be poured over it at once to effect the decomposition of the glyceryl trinitrate. *Dosage:* 0.06 cc. (1 minim) dropped on the tongue, or taken after diluting with water.

Glyceryl Trinitrate Tablets, *Tabellae Glycerylis Trinitratis*, U.S.P. (Nitroglycerin Tablets, Trinitrin Tablets). The usual sizes contain 0.3 mg., 0.4 mg., 0.6 mg., and 1.2 mg. *Dosage:* 0.4 mg. glyceryl trinitrate.

Papaverine

Papaverine, $C_{20}H_{21}O_4N$, an alkaloid obtained from opium and belonging to the benzyl isoquinoline group, was first advocated for relief of smooth muscle spasm by Pal, of Vienna.

It is marketed as the water-soluble hydrochloride. Its toxicity is very low. It is contained in opium and thus comes under the Federal Narcotic Regulations, although it is free of narcotic action.

Pharmacological Action.—Papaverine is a rather feeble central analgesic and a local anesthetic. Its toxicity is low, and neither tolerance nor habituation has been reported.

In contrast to morphine the actions of papaverine on the central nervous system are negligible, and the drug causes neither sleep nor analgesia in therapeutic doses. Papaverine relaxes smooth muscles of the body, especially those of blood vessels. This relaxation occurs particularly if spasm exists. The muscles responding to this drug are those of the bronchi, gastrointestinal tract, ureters, biliary system, and blood vessels, including the coronary arteries. Papaverine is not nearly as effective as epinephrine in bronchial asthma, but it may be given intravenously in large doses, with a wide margin of safety. It has mild sedative action. It is not a myocardial depressant.

Therapeutic Uses.—Pal recommends the use of papaverine in various spasmodic conditions of the smooth muscle, including gastric and intestinal spasms, in biliary colic and in bronchial spasm. Of more doubtful value is its use in pertussis, hyperemesis and vascular spasm, acute uremia, and eclampsia. The local anesthetic action, with vasodilatation, has been used against rhino-asthma, and to mitigate the pain of irritant injections. *Dosage:* The oral and hypodermic single dose is from 0.03 to 0.08 Gm. (½ to 1⅓ grains); daily dose to 0.5 Gm. (7½ grains). Single doses of even 1 Gm. (15 grains) are said to be nontoxic (N.N.R.).

At the present time the clinical use for papaverine is in the treatment of conditions associated with smooth muscle spasm; e.g., peripheral vascular embolism, pulmonary embolism, Reynaud's disease, and ureteral or other types of tubular spasm. Its oral administration may prove useful in the treatment of heart disease.

Good therapeutic results have been obtained by papaverine in patients with peripheral or *pulmonary embolism.* When given intravenously it has prevented amputation of limbs and has preserved life. The drug acts by increasing collateral circulation in reflexly constricted vascular beds. Symptoms such as pain and paresthesia may be completely relieved after the intravenous injection of 20 to 100 mg. of papaverine hydrochloride. Threatened *gangrene* from ergotamine tartrate poisoning is apparently successfully prevented by the use of 0.03 Gm. (½ grain) of papaverine hydrochloride administered intravenously or orally over a period of several days. A combination of codeine sulfate 0.015 Gm. (¼ grain) and papaverine hydrochloride, 0.015 Gm. (¼ grain) has been found valuable in the treatment of nasal discharge and congestion of *catarrhal fever.*

Heart Disease.—According to Katz (1948) papaverine has a definite place in the treatment of coronary heart disease. It is a powerful coronary vasodilator, it is sedative and is a soothing agent on ectopic pacemakers. For chronic coronary heart disease the dose of papaverine

should be begun at 1 Gm. three to four times a day, orally, and should be increased until the effect desired is obtained or until side reactions indicate stoppage of the drug.

Oral papaverine in doses of 0.1 Gm. (1½ grains), three or four times a day, has proved highly successful in the treatment of the *angina syndrome.* Intravenously administered papaverine in doses of 0.06 to 0.1 Gm. (1 to 1½ grains) causes temporary abolition or reduction in the number of *premature systoles,* the effect lasting from two to ten minutes. Oral papaverine in doses up to 3 grains, four or five times a day, has an effect in eradicating or reducing the frequency of premature auricular, nodal, or ventricular systoles (Eleck, Katz, 1942).

Preparations

Papaverine Hydrochloride, *Papaverinae Hydrochloridum,* U.S.P. *Dosage:* Oral and intravenous, 0.1 Gm. (1½ grains).

Papaverine Hydrochloride Injection, *Injectio Papaverinae Hydrochloridi,* U.S.P. A sterile solution of papaverine hydrochloride in water for injection. *Dosage:* Intravenous 0.1 Gm. (1½ grains).

Xanthine Derivatives

The xanthine derivatives are of value in the treatment of heart disease because of their diuretic action and also because of their mild stimulatory action on the myocardium.

The xanthines have been used for many years in the treatment of angina pectoris. Aminophylline (theophylline ethylenediamine) is probably the most widely used xanthine preparation in heart conditions. It is quite soluble and there is evidence that ethylenediamine enhances the vasodilator effect of theophylline. For detailed discussion of xanthine, see chapter on Diuretics.

Therapeutic Uses.—In *angina pectoris* the value of *an* xanthine dilator is questionable. Theobromine with sodium acetate, 0.5 Gm. three times a day, may be of value.

Congestive Heart Failure.—Xanthines may be of value on the basis of their diuretic and possibly their direct stimulating action on the myocardium. Various xanthine preparations may be given. Aminophylline, 1½ to 3 grains (0.1 to 0.2 Gm.) may be given three times daily by mouth. This drug may be given by vein or intramuscularly or as a retention enema. Aminophylline, 0.25 to 0.5 Gm. intravenously, may also be used every four to eight hours to control *Cheyne-Stokes breathing.*

Extrasystoles may occasionally respond to coronary dilators. Aminophylline may be tried orally for this condition in average dosage.

Thiocyanates

Various drugs have been used for the treatment of hypertension. The majority are of questionable value. Potassium thiocyanate has been used for the treatment of this condition. The continued administration generally leads to persistent lowering of the blood pressure in normal individuals, in three-fifths of the patients with glomerular nephritis, and in about a third of the patients with hypertension.

Pharmacological Action.—The thiocyanate ion is similar in effect to the iodine ion. When taken orally a high percentage of the drug is found in the extracellular fluid and thus influences the aggregation of colloids in a manner similar to the iodides. It is excreted primarily by the kidneys.

Potassium thiocyanate in moderate dosage has a sedative action. Large doses produce symptoms varying from mild drowsiness to toxic psychosis. Certain effects on blood have been reported, such as reduction of erythrocyte count, hemoglobin, serum proteins, and cholesterol. It produces smooth muscle relaxation. The drug does not increase peripheral blood flow nor does it produce peripheral dilation. Cardiac depression, increased cardiac output and decrease in the size of the heart have been reported.

Therapeutic Uses.—*Hypertension.*—The mechanism of the fall in blood pressure is obscure. Kessler and Hines (1948) suggest that the hypertensive action may be an effect produced by breakdown products of the drug in vivo. There is practically no fall unless the blood level of thiocyanate is held at 8 to 12 mg. per cent for prolonged periods. As low concentrations are ineffective and higher concentrations are toxic, the level of the blood must be checked chemically. The average dose is 0.3 Gm. daily in a single dose, but this may need to be increased to 0.6 Gm. or 0.9 Gm. daily to furnish adequate blood level. Patients should be seen at least once a week for blood thiocyanate estimations.

Most patients complain of marked fatigue following thiocyanate therapy. Many feel drowsy even though there is no change in blood pressure. This, according to Barker (1935), wears off in a few weeks. Vertigo is common, and some complain of cramps and weakness in the arms and legs. Nausea and vomiting are among the first symptoms of toxicity. Gastrointestinal symptoms are rare, however, if the level of thiocyanates is kept below 21 mg. per 100 cc. of blood.

Thiocyanate therapy is not widely used; the rationale is not clear and the effects are seldom very encouraging.

References

Digitalis

Carroll, F. D.: Visual Symptoms Caused by Digitalis, Am. J. Ophth. **28**: 373, 1945.

Carter, T. B.: Uses and Abuses of Digitalis, M. Clin. North America **27**: 143, 1943.

Christian, H. A.: The Pharmacology of Digitalis in Relation to the Therapy of Heart Disease, New England J. Med. **208**: 66, 1933.

Cushny, A. R.: Digitalis and Its Allies, London, 1925, Longmans Green and Co.

DeGraff, A. C.: Clinical Comparison of the Cardiac Glycosides, New York State J. Med. **45**: 1803, 1946.

Gold, H.: Pharmacologic Basis of Cardiac Therapy, J. A. M. A. **132**: 547, 1946.

Herrmann, G. R., Decherd, G. M., and McKinley, W. F.: Digitalis Poisoning, J. A. M. A. **126**: 760, 1944.

Hueper, W. C.: Some Toxic Aspects of Digitalis Therapy, New York State J. Med. **45**: 1442, 1945.

Luten, D.: The Clinical Use of Digitalis, Springfield, Ill., 1936, Charles C Thomas.

Movitt, E. R.: Digitalis and Other Cardiotonic Drugs, New York, 1946, Oxford University Press.

Withering, William: An Account of the Foxglove and Some of Its Medical Uses, Birmingham, 1785.

Withering, William: An Account of the Foxglove and Some of Its Medicinal Uses; With Practical Remarks on Dropsy and Other Diseases, London, 1785. Reprinted in Medical Classics **2**: 305-443, 1937.

Quinidine

Carter, J. B.: Uses and Abuses of Quinidine, M. Clin. North America **29**: 215, 1945.

Findlay, G. M.: Recent Advances in Chemotherapy, Philadelphia, 1939, The Blakiston Co.

Katz, L. N.: Quinidine, J. A. M. A. **136**: 1028, 1948.

Levine, S. A.: Clinical Heart Disease, Philadelphia, 1936, W. B. Saunders Co.

Lewis, Sir Thomas: Diseases of the Heart, ed. 2, New York, 1937, The Macmillan Co.

Lewis, T., Drury, A. N., Iliescu, C. C., and Wedd, A. M.: The Manner in Which Quinidine Sulfate Acts in Auricular Fibrillation, Brit. M. J. **11**: 514, 1921.

Sagall, E. L., Horn, C. D., and Riseman, J. E. F.: Studies on the Action of Quinidine in Man, 1. Measurement of the Speed and Duration of the Effect Following Oral and Intramuscular Administration, Arch. Int. Med. **71**: 460, 1943.

Smith: Quinidine in the Treatment of Cardiac Irregularities, J. A. M. A. **78**: 877, 1922.

Sollmann, T.: Manual of Pharmacology, ed. 8, Philadelphia, 1948, W. B. Saunders Co.

Stroud, W. D., and Laplace, L. B.: Significance and Treatment of Auricular Fibrillation, Internat. Clin. **1**: 13, 1935.

White, P. D.: Heart Disease, New York, 1937, The Macmillan Co.

Nitrites

Crandall, L. A., Jr., Leake, C. D., Lovenhart, A. S., and Muehlberger, C. W.: Acquired Tolerance to and Cross Tolerance Between the Nitrous and Nitric Acid Esters and Sodium Nitrite in Man, J. Pharmacol. & Exper. Therap. **41**: 103, 1931.

Gold, H., Kwit, N. T., and Otto, H.: Xanthines (Theobromine and Aminophylline) in Treatment of Cardiac Pain, J. A. M. A. **108**: 2173-2179, 1937.

Lueth, H. C., and Hanks, T. G.: Unusual Reaction of Patients With Hypertension to Glyceryl Trinitrate, Arch. Int. Med. **62**: 97-108, 1938.

Marshall, C. R.: The Mode of Action of Nitric Esters, J. Pharmacol. & Exper. Therap. **83**: 106, 1945.

Papaverine

Elek, S. R., and Katz, L. N.: Some Clinical Uses of Papaverine in Heart Disease, J. A. M. A. **120**: 434, 1942.

de Takats, G.: The Use of Papaverine in Acute Arterial Occlusions, J. A. M. A. **106**: 1003, 1936.

Xanthine Derivatives

Boyer, N. H.: Aminophylline and Related Xanthine Derivatives, Present Status and Therapeutic Claims, J. A. M. A. **122**: 306, 1943.

McMahon, A., and Nussbaum, R. A.: The Use and Abuse of Theophylline and Its Derivatives, South. M. J. **33**: 1127, 1940.

Smith, F. M., Rathe, H. W., and Paul, W. D.: Theophylline in the Treatment of Disease of the Coronary Arteries, Arch. Int. Med. **56**: 1250, 1935.

Thiocyanates

Barker, M. H., Lindberg, H. A., and Wald, M. H.: Further Experiences With Thiocyanates, Clinical and Experimental Observations, J. A. M. A. **117**: 1591, 1941.

Barker, M. H.: Some Uses and Abuses of the Thiocyanates, Texas State J. Med. **42**: 462, 1946.

Forster, R. E.: The Medical Use of Thiocyanates in the Treatment of Arterial Hypertension, Am. J. M. Sc. **206**: 668, 1943.

Kapernick, J. S.: The Blood Pressure in Essential Hypertension; Effect of Several Reputedly Hypotensive Drugs, Am. Heart J. **26**: 610, 1943.

Kessler, D. L., and Hines, L. E.: Thiocyanate Therapy in Hypertension, J. A. M. A. **138**: 549, 1948.

Nelson, E. E.: Thiocyanates, Internat. M. Digest 41: 245, 1942.

CHAPTER XVI

OXYTOCIC DRUGS

Oxytocics are drugs which initiate or enhance uterine contractions. The uterus, which contains smooth muscle, contracts spontaneously and rhythmically. The contractions are marked when the uterus is fully developed and its activity varies with different periods of the menstrual cycle.

Although innervated by both cholinergic and adrenergic fibers, the responses of the uterus to stimulation from these nerves and to autonomic drugs is not marked and varies in different species and in the pregnant and nonpregnant state. Furthermore, complete denervation of the uterus causes little or no change in motor activity. Obviously, the action of autonomic drugs on the uterus are of no great practical significance.

The oxytocic drugs are a group of drugs with marked effect on uterine motility. There are definite indications for the clinical use of oxytocics. In brief, they are as follows: (1) to induce labor at term if necessary, (2) to control postpartum hemorrhage arising from uterine atony, and (3) to aid and hasten normal involution of the uterus during puerperium.

The most important of these drugs are ergot and its alkaloids, and posterior pituitary. Quinine has long been popular for the induction of labor. Its oxytocic effect, however, is unreliable. Other drugs can effect uterine motility but the ergot alkaloids and posterior pituitary are the most useful clinical oxytocics.

Oxytocic drugs should never be used during the first and second stages of labor. Their routine use for initiating or hastening labor for the convenience of the physician is regrettable since violent contractions may cause injury to the fetus and cripple the uterus. In conservative obstetric practice they are used only at the end of the third stage of labor and during puerperium to control postpartum bleeding and hasten involution of the uterus.

ERGOT

Ergot preparations have enjoyed a time-honored place in obstetrical practice. Of these preparations, fluidextract of ergot and ergonovine are of great importance in therapeutics because of their ability to stimulate the uterus and prevent postpartum hemorrhage.

Ergot, a parasitic fungus *(Claviceps purpurea)* which grows usually on rye and on certain grasses, was the first authentic oxytocic drug introduced into medicine. The medicinal properties of this fungus, the consumption of which resulted in widespread epidemics of "ergotism," were known to early European midwives. These epidemics of ergotism were usually characterized by the direct development of gangrene of the extremities.

Stearns (1807) was the first to introduce its use in obstetrics. Recent investigators, among whom are Barger and Dale and their coworkers, have made a thorough study of the chemistry of ergot and have shown it to contain several potent alkaloids, including ergotoxine, ergotamine, and ergonovine; at least four amines, and acetylcholine and other choline derivatives. These active substances are found in

ergot in varying amounts. From the therapeutic point of view the most important of these compounds are the alkloids *ergotoxine, ergotamine,* and *ergonovine* (ergometrine).

Pharmacological Action.—Ergot acts chiefly on the smooth musculature of the uterus and blood vessels, both of which it causes to contract. The oxytocic, emmenagogic, and homostatic actions of ergot are of importance in therapeutics. When taken orally ergot is rapidly absorbed; its action becomes manifest in fifteen to twenty minutes and lasts about one hour. The fate of the active principles is unknown.

Local Action.—When applied locally to mucous membranes, ergot acts as a mild hemostatic and astringent irritant.

Action on Uterus.—The most important action of ergot is on the uterus where it causes powerful contractions alternating with periods of relaxation. The action is peripheral, being exerted mainly through the sympathetic nerves in a manner similar to its action on blood vessels. Direct action of ergot on smooth muscle may be demonstrated in the eye, where the muscle contracts, but after ergot, atropine does not cause dilation. In labor, small doses accelerate and strengthen contractions, while large doses prolong uterine contraction.

Action on Muscles.—Ergot tends to favor cardiac contraction, peristalsis, etc., through its specific stimulating action on involuntary muscle. The bladder, the pupil, and other structures possessing a similar type of muscle, respond to ergot.

Action on Circulation.—Therapeutic doses cause a rise in blood pressure, mainly through constriction of the peripheral vessels by direct action upon them, and by slight stimulation of the vasomotor center. The heart rate may be slowed and the amplitude increased by stimulation of the cardioinhibitory center.

Ergot may produce gangrene of the extremities. Some attribute this to vasoconstriction, while others believe it to be due to formation of emboli which obstruct circulation.

Toxicology.—Most cases of ergot poisoning are due to an overdose of the drug, eating bread made from infected rye, or to its use as an abortifacient.

Acute Poisoning.—The symptoms of acute ergot poisoning appear in a few hours and are characterized by vomiting, thirst, diarrhea, and tingling of the extremities. Uterine hemorrhage and abortion may occur if the individual is pregnant. The face and limbs swell; the skin becomes pale and the surface temperature falls; abnormal sensations develop in the skin and twitching of the muscles occurs. Later, there is a fall of temperature, associated with anuria, convulsions, and coma. Death occurs from cardiac and respiratory paralysis.

Chronic Poisoning.—Chronic ergot poisoning, which was commonly quite prevalent, is now relatively rare where modern grain-cleaning machinery is used. The chronic toxic effects take two forms: the first form is known as the *gangrenous form,* characterized by dry gangrene in the extremities and cataracts on the eyes. In this type the symptoms are tingling, formication, redness, coldness, eruption of vesicles containing a dark fluid, and finally dry gangrene. The extremities may fall off with little pain or hemorrhage. Gangrene may occur in the intestine, causing perforation and peritonitis. The second form, the *spasmodic variety,* is characterized by initial symptoms of vertigo, tinnitus, headache, formication, and often mental depression. Later, muscular tremors and contractures, especially of the flexors of the fingers and toes, appear. The prognosis for this type is poor.

The *fatal dose* varies, but may range from 15 to 60 grains or more. *Postmortem lesions* of ergot, aside from areas of gangrene, are not characteristic. Hyperemia may be noted throughout the kidneys, uterus, liver, and lungs. Pieces of fungus found in the stomach aid in making the diagnosis.

TREATMENT OF ERGOT POISONING.—In *acute poisoning*, wash out the stomach with sodium bicarbonate. Empty the bowels with soapsuds enemas and such purgatives as castor oil or Epsom salts. Give tannic acid internally. Administer stimulants such as strychnine and coffee. In *chronic poisoning* the treatment is symptomatic. Saline intravenously and hypodermically is indicated. Amputation may be the treatment of choice for the gangrenous type.

Therapeutic Uses.—In labor the fluidextract may be employed. When the use of ergot is to be continued for some time, its administration in capsules is to be recommended. In obstetrics, its use by needle may be desired; if so, commercial preparations put up in sterile ampules are available on the market.

Obstetrics.—In parturition ergot is used to (1) promote uterine contractions, (2) to prevent postpartum hemorrhage, and (3) in subinvolution of the uterus. Ergot is largely used in obstetrics to *promote contraction* of the uterus. When the proper dose is administered, and the cervix is dilated, the drug tends to hasten normal delivery. The drug may be given orally, being effective in fifteen to thirty minutes. For the prevention of *postpartum hemorrhage*, the drug may be given as soon as the second stage of labor terminates, but should not be given until the placenta has been expelled. A dose of 2 to 5 cc. of the fluidextract is given subcutaneously or intramuscularly to arrest postpartum hemorrhage. Its use during labor may predispose to rupture of the uterus or asphyxia of the child. In *subinvolution* or failure of the uterus to return to normal size after childbirth ergot may be used to contract the uterus.

In Hemorrhage.—Ergot is used to treat internal hemorrhages of various types. It is, no doubt, administered in too small a dose to affect the blood pressure. It has been suggested in pulmonary hemorrhage, because it contracts the blood vessels and tends to favor clotting, but clinical evidence to support its use is lacking. Ergot is also used for hemorrhage from the uterus in menorrhagia. Ergot is a time-tried remedy for excessive bleeding in young girls just starting to menstruate. Its use for hemorrhage from other internal organs is not rational.

In treatment of menorrhagia, etc.:

Strychnine Sulfate	0.03 Gm. (gr.ss)
Hydrastine Hydrochloride	0.65 Gm. (gr.x)
Ergot Extract	2.50 Gm. (gr.xl)

M. ft. caps. No. xx.
Sig.: One, two hours after meals.

As Circulatory Stimulant.—Ergot as a circulatory stimulant deserves more popularity than it has received. It is especially indicated in chronic vasomotor relaxations, such as cerebral congestion, colliquative sweats, relaxing diarrhea, etc.

Standardization of Ergot Preparations.—All ergot preparations, especially those containing moisture, deteriorate with age. It is necessary therefore to standardize them, and the date of assay should be indicated on the container.

Ergot is assayed officially in this country by the cockscomb method which measures the total pharmacologically active alkaloids. Ergot

Fluidextract, N.F., is standardized biologically by the production of cyanosis in the combs of white Leghorn roosters. The roosters are first standardized for color production by a standard fluidextract of known potency.

PREPARATIONS

Ergot, *Ergota,* N.F., B.P. *Dosage:* 2 Gm. (30 grains).

Ergot Fluidextract, *Fluidextractum Ergotae,* N.F. Ergot (100%), alcohol (40%). *Dosage:* 2 cc. (30 minims). *Extractum Ergotae Liquidum,* B.P. *Dosage:* 10-20 minims.

Ergot Extract, *Extractum Ergotae,* N.F. *Dosage:* 0.5 Gm. (8 grains).

Ergot Aseptic, N.N.R. This is an aseptic liquid of ergot, standardized biologically to the same potency as Ergot Fluidextract. *Dosage:* 1 to 2 cc. (15 to 30 minims) intramuscularly.

OTHER ERGOT CONSTITUENTS

Ergonovine (Ergometrine)

Communications from four laboratories have been published, reporting the isolation of a new oxytocic alkaloid from ergot. The Council of Pharmacy and Chemistry of the American Medical Association adopted the new, nonproprietary name "ergonovine." In Great Britain this preparation is known as *ergometrine.*

Ergonovine comes under the broad definition of an alkaloid, with the formula, $C_{19}H_{23}O_2N_3$. It is a colorless, crystalline material and is water soluble. Ergonovine salts are relatively stable. This alkaloid may be assayed by the cockscomb response.

Pharmacological Action and Uses.—Ergonovine shares with ergotamine and ergotoxine the property of causing uterine stimulation. The character of the contractions is similar to that described for ergot. Ergonovine, however, is much more rapid in action, for the uterine response occurs almost immediately after intravenous injection and within a few minutes after intramuscular or oral administration. Ergonovine differs from ergotoxine and ergotamine in that it is readily absorbed from the gastrointestinal tract. It shares with ergotamine and ergotoxine the ability to produce gangrene.

Oxytocic Action.—When administered, in doses of from 0.2 to 0.4 mg. by mouth, it causes typical ergot response in a few minutes. Two tablets, each containing 0.2 mg. of ergonovine maleate, every four hours for six doses, and then three times a day for three or four days serve as a satisfactory post-partum prophylactic against hemorrhage. Favorable uterine response continues for from two to three hours. Intravenous administration of the same amount causes immediate response, characterized by great tonicity of action.

In the Chicago Lying-in Hospital it is customary to give 0.2 mg. of ergonovine intravenously as soon as the head is delivered. The uterus contracts quite promptly, which assists in separation and delivery of the placenta. This reduces the duration of the third stage of labor. The effects of this drug apparently last from four to six hours.

Migraine.—Ergonovine is less effective than ergotamine, although the reverse is occasionally true when administration is by the oral route. It causes less nausea and vomiting than ergotamine and is also useful in patients who complain of severe paresthesias following ergotamine. Ergonovine is contraindicated during pregnancy because of its strong oxytocic action. The dosage and method of administration are the same as for ergotamine.

The drug produces no untoward symptoms; it has very little or no effect on blood pressure and pulse. There is apparently no cumulative action, and its toxicity is extremely low. Crystals of the drug are stable, while the aqueous solution tends to deteriorate. The powder is therefore best dissolved in water just before administration.

Stimulant of Sympathetic System.—Ergonovine is a stimulant of the sympathetic system (not a depressant). Unlike ergotoxine and ergotamine it has little inhibitory action on epinephrine. Ergonovine maleate shows little toxicity. The stimulating effect on the sympathetic system is evidenced by the mydriasis on instillation into the rabbit's eye. In large doses respiration is depressed.

PREPARATIONS

Ergonovine Maleate, *Ergonovinae Malcas,* U.S.P. *Dosage:* Intravenous or intramuscular, 0.2 mg. oral, 0.5 mg. (U.S.P.).

Ergonovine Maleate Injection, *Injectio Ergonovinae Maleatis,* U.S.P. A sterile solution of ergonovine maleate in water. *Dosage:* Intravenous or intramuscular, 0.2 mg. of ergonovine maleate.

Ergonovine Maleate Tablets, *Tabellae Ergonovinae Maleatis,* U.S.P. Usual sizes contain 0.2 mg. and 0.5 mg.

Less Important Ergot Constituents

Amines.—Amines are decomposition products of proteins and probably do not exist in fresh ergot.

Tyramine ($OH.C_6H_4CH_2.CH_2NH_2$), parahydroxyphenylethylamine, like epinephrine, is a stimulant of sympathetic nerves. This action leads to a rise in blood pressure, but is not materially concerned in the uterine action.

Histamine ($C_3H_3N_2(CH_2)_2NH_2$), beta-imidazolylethylamine, lowers blood pressure and stimulates the uterus.

Acetylcholine, $(CH_3)_3N.OHCH_2CH_2OCOCH_3$, a poisonous combination of acetic acid and choline occurring in ergot, is responsible for cardiac inhibition and blood pressure lowering caused by ergot.

PITUITARY (POSTERIOR LOBE)

The Pituitary Body.—The pituitary body or hypophysis cerebri is embryologically and chemically a highly complex structure. It consists of four component parts: the pars anterior, the pars intermedia, the pars nervosa, and the pars tuberalis. Functionally, it can be divided into the anterior lobe (pars anterior), and the posterior lobe, made up of the pars intermedia and the pars nervosa. Little is known of the pars tuberalis. Extracts of the anterior and posterior lobes display striking pharmacological properties.

The nature of the active principles of the posterior lobe of the pituitary has been a matter of some dispute. Oliver and Schafer (1895) first observed the pressor effects of an extract of the posterior lobe. Dale (1910) demonstrated its oxytocic action, and Bell (1909) made use of this action in obstetrics, thereby introducing one of our most important therapeutic agents. Kamm and his co-workers (1929) separated the posterior pituitary extract into a fraction containing the oxytocic principle, "pitocin," and one containing the diuretic and pressor principles, "pitressin." It seems established now that there are at least two important principles in the posterior pituitary lobe. These principles are:

1. *Pitocin.*—Pitocin represents the oxytocic principle (alphahypophamine) of the posterior lobe, relatively free from pressor substance. Clinical experience with pitocin has shown that it is a satisfactory pituitary preparation for obstetrical use. It is used for stimulation of uterine contractions, in doses of 0.3 to 1 cc. intramuscularly. It is preserved with 0.5 per cent chlorobutanol. There has been some indication that it acts rather more rapidly than the previously known posterior lobe extracts containing both principles. This may be due to the slightly more rapid absorption caused by the absence of local vasomotor effects.

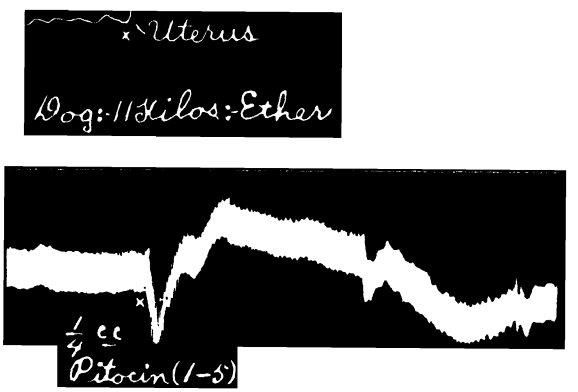


Fig. 27.—Uterus tracing, blood pressure, and respiration showing the action of pitocin. Previous injections had been made. The uterine effect is mainly that of increased tonus. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

2. *Pitressin.*—This substance, betahypophamine, produces a rise of blood pressure by acting directly on the arterioles, causing vasoconstriction. Other actions are its ability to contract smooth muscle, and its diuretic and antidiuretic action. The diuretic action may be due to the vasopressin action causing an increase in urine secretion, while the antidiuretic action is thought to be due to an active principle distinct from that which acts on the blood

pressure but is contained in the vasopressin fraction. In diabetes insipidus the administration of pitressin causes a temporary inhibition of urinary secretion.

SOLUTION OF POSTERIOR PITUITARY, U.S.P., contains all the water-soluble principles of the posterior lobe. It may also contain variable quantities of nonspecific depressor substances which may cause a transitory fall in blood pressure; these substances are of no clinical importance but may be the source of error in experimental work.

Pharmacological Action.—*Absorption and Excretion.*—Pituitary extract is readily absorbed following hypodermic injection. Oral administration of the gland is ineffective. The excretion of pituitary principles is slow and occurs principally through the kidneys.

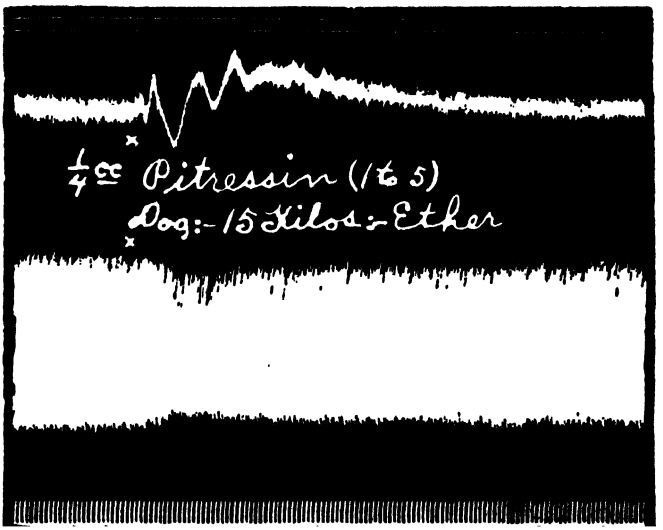


Fig. 28.—Blood pressure and respiration showing the action of a small dose of pitressin given after a previous very large dose. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

Action on the Uterus.—The strongest and most important action of pituitary extract is on the uterus, which responds by increased motor activity, increase in tonus (Fig. 27), initiation of reinforcement of contractions, or by firm spasm. The action of pituitary extract in the intact animal and in human beings varies somewhat from the action in the isolated uterus submerged in a warm saline bath. The action in situ is apparently modified by various factors, such as the condition of the uterus, whether it is in the nonpregnant or pregnant state, or whether in the early or late stage. The organ responds more strongly to pituitary if it is in the actively contracting state, and the uterus seems more responsive in late pregnancy and during labor. The action on the uterus is more marked than the motor action on the alimentary tract.

Action on Urine Flow.—In man and unanesthetized animals pituitary extract decreases urinary flow, an action which is especially pronounced in diabetes insipidus. The hypodermic injection of pituitary extract reduces the urine output of ten to fifteen liters to a normal output, and by repeated injections the normal output may be retained, but the diuresis returns on stopping the drug.

The *antidiuretic* action may be due to lessened glomerular activity or to an increased reabsorption of the fluid as it passes over the tubules. Some investigators feel that the action is probably due to increased reabsorption located in the loop of Henle.

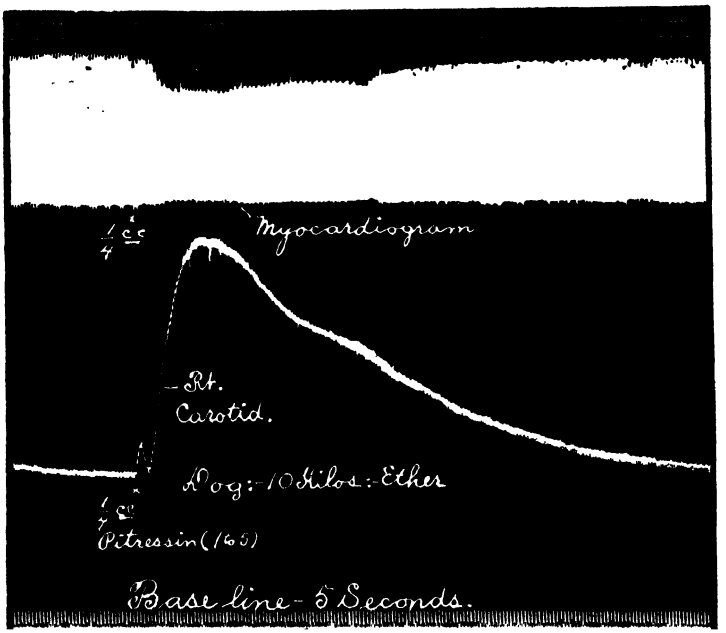


Fig. 29.—Myocardium and blood pressure showing action of pitressin. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

Action on Milk Secretion.—Pituitary extract is an effective galactagogue, increasing the rate of milk secretion by eighty to one hundred times. The action apparently is directly on the unstriated muscles of the gland, as the results occur even if the secretory nerves are cut. This is not prevented by atropine, the muscle fibers being affected directly. Extracts of pituitary cause a tingling of the breasts and produce a secretion even in nonpregnant mammals. The increase sometimes is only temporary and may be followed by a corresponding decrease of secretion.

Action on the Stomach, Intestine, and Bladder.—The tone of these organs is increased, and relaxation is less complete. In the dog the pressor factor seems to be more important in its effect upon the intestine than the oxytocic principle. Pituitary relieves postoperative gas dis-

tention, an action which is less powerful than that of pilocarpine. The vesical muscle is stimulated by hypodermic injection of pituitary extract.

Action on Circulation: Action on Heart.—The rate of the heart is slowed by the pressor reflex. The contractions of excised hearts are strengthened by pituitary extracts; but in intact animals cardiac action is depressed by diminution of oxygen supply following coronary constriction. The extract also slows the excised heart perfused with Ringer's solution, which indicates that the muscle may be directly affected.

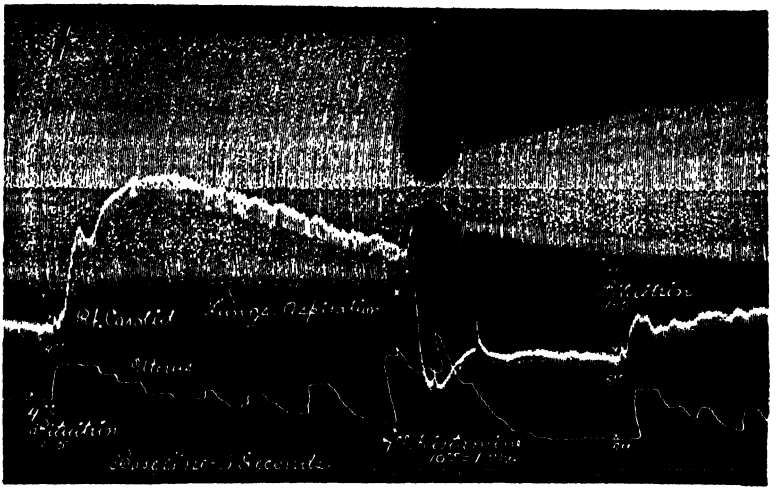


Fig. 30.—Lung volume, blood pressure, and uterine tracings in a pithed dog, showing the action of pituitrin, histamine, and a second injection of pituitrin. The object of the experiment was to determine whether pituitrin caused either bronchoconstriction or bronchodilatation. Apparently neither action occurs if the drug is free from certain impurities. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

Action on Blood Pressure.—Injections of posterior lobe preparations produce usually a rise in arterial pressure; in a certain number of persons, however, the rise may be slight and in some cases a definite lowering may occur. The effect of pitressin on the blood pressure is shown in Figs. 28 and 29. Pituitary action differs from epinephrine in that (1) it appears to be independent of nerve supply; (2) the action is not antagonized by ergotamine; (3) there is no acceleration of the heart, even after vagi section; (4) the constriction of the arterioles is accompanied by an increase in tone of the capillaries; (5) the rise is not as high as that obtained with epinephrine, but is more sustained. If large doses are repeated at short intervals, the rise becomes progressively smaller, and the depressor effect becomes more prominent.

Action on Central Nervous System.—Somnolence and muscular weakness follow large doses of pituitary. The cerebrospinal fluid is increased apparently from a direct action on the choroid plexus. The action of

pituitary is, no doubt, a direct action on the terminal organs rather than on the nervous mechanism.

Action on Respiration.—Initial injections of pituitary extract cause respiration to become strengthened temporarily (Fig. 27) then depressed, respiration becoming slower and shallower. This action is thought to be directly on the respiratory center. Pituitrin apparently has no bronchoconstrictor or bronchodilator action (Fig. 30).

Toxicology.—Toxic effects are rare in the use of pituitary. Symptoms of toxicity are tinnitus, anxiety, convulsions, mydriasis, and diarrhea. Rupture of the uterus and asphyxia of the fetus have occurred.

Therapeutic Uses.—The posterior lobe of the pituitary gland is available for administration as the dried substance obtained from the gland of the ox, and also as the solution of posterior pituitary. It is principally used hypodermically. The aseptic ampules of the solution are employed almost exclusively.

Obstetrics.—Solution of posterior pituitary is a powerful drug which when handled uncautiously in labor may prove dangerous to both mother and child. There are, however, certain rational indications for its use in obstetrics. First, in the abortion of early pregnancy to avoid or assist surgical evacuation of the uterus; second, in the medical induction of labor with castor oil and sometimes quinine, provided that only small doses (0.1-0.5 cc.) are used at thirty-minute intervals and that the drug is stopped the minute the uterus responds; third, in uncomplicated cases of primary uterine inertia; fourth, in certain cases of abruptio placentae or atonic antepartum hemorrhage; and fifth, in atonic postpartum bleeding, where it may be given in larger doses intravenously or intramuscularly.

The following are the views of Hirst in regard to pituitary therapy in obstetrics.

1. "Its routine use after third stage of labor is to be avoided and its administration only resorted to in case of hemorrhage and atony of uterine muscle.
2. "It should be given in primiparae for inertia uteri only when the head has passed the cervix.
3. "It should be given in multiparae only when the cervix is thoroughly effaced, fairly dilated and easily dilatable.
4. "It should never be given to any patient, if there is an obstacle to an easy delivery.
5. "One-half mil doses are as effective as one mil and superior."

Pituitrin in small doses is effective and safe when used to *induce labor* if it is indicated. The dose used should not exceed three minims, repeated three or four times at hour intervals.

Diabetes Insipidus.—This condition responds to pituitary extract in about 90 per cent of the cases. The solution should always be injected hypodermically or intramuscularly, but some absorption occurs when it is applied to the nasal mucous membrane. Hypodermic injection diminishes thirst and output of urine. When pituitrin is withheld, the output rises.

Administer 1 cc. of the obstetrical pituitrin, or of pitressin. The duration of relief varies from four to forty-eight hours. It is well to administer the injection at night in order to have a period of freedom during the sleeping hours. Since peristalsis is often increased by pituitrin, it is advisable to give the injection about two hours before bedtime in order to permit bowel movement before retiring.

Shock and Collapse.—Pituitary has been recommended in shock and in various stages of collapse, but it is ineffective in advanced shock, and is, at best, of only temporary value in incomplete shock. Pituitary is useful in raising the blood pressure. An injection of 1.0 to 2.0 c.c. of the official solution of posterior pituitary is recommended. The action is stronger than that of epinephrine but is often disappointing.

PREPARATIONS

Posterior Pituitary, *Pituitarium Posterius,* U.S.P. The posterior lobe obtained from the pituitary body of cattle. *Pituitarium,* B.P.

Posterior Pituitary Injection, *Injectio Pituitarii Posterioris,* U.S.P. *Dosage:* By hypodermic injection, 1 cc. (15 minims).

Ampules of Pitocin, N.N.R. An aqueous solution of oxytocic principle of posterior lobe of the pituitary gland, having an activity on the uterus equal to that of U.S.P. Solution of Posterior Pituitary. *Dosage:* 0.3 to 1 cc. (5 to 15 minims) intramuscularly.

Ampules of Pitressin, N.N.R. Aqueous solution of the pressor and diuretic-antidiuretic principle of the posterior lobe of the pituitary gland having a pressor activity twice that of U.S.P. Solution of Posterior Pituitary, and equal to that of the "Surgical Solution." *Dosage:* 0.3 to 1 cc. (5 to 15 minims) intramuscularly.

QUININE

The use of quinine has a rather undeserved reputation as an oxytocic. The uterus, *in situ* or excised, is stimulated by quinine in moderate doses and depressed by large amounts. Clinical doses produce little or no effects, unless labor pains have started. Although quinine has been used with other adjuncts to initiate labor, it cannot be considered a potent and reliable uterine stimulant.

It has been claimed that the administration of quinine (0.65 Gm.) preceded by two ounces of castor oil induces labor at term and hastens uterine involution (Baily, 1926). The action probably is due to the castor oil, because quinine is administered freely in malarial districts without fear of causing abortion.

Quinine rarely produces toxic actions if the dose is limited to 0.6 Gm. The drug may pass through the placental barrier and cause toxic effects in the fetus. If quinine is used to intensify labor pains, it should be restricted to patients at or beyond term. It has been recommended that small doses of posterior pituitary be administered following quinine. (See further discussion of Quinine under Antimalarial Drugs.)

References

Ergot

Adair, F. L., and Pearl, S.: Present Status of Oxytocics in Obstetrics, J. A. M. A. 107: 261, 1936.

Barger, G.: Ergot and Ergotism. London and Edinburgh, 1931, Gurney and Jackson.

Comfort, M. W., and Erickson, C. W.: Untoward Effects From Use of Ergot and Ergotamine Tartrate, Ann. Int. Med. 13: 46-60, 1939.

Glandular Physiology and Therapy, Chicago, 1935, American Medical Association.

Moir, C., and Russell, C. S.: An Investigation of the Effect of Ergot Alkaloids in Promoting Involution of the Postpartum Uterus, J. Obst. & Gynaec. Brit. Emp. 50: 94, 1943.

Nelson, E. E., and Calvery, H. O.: The Present Status of the Ergot Question, Physiol. Rev. 18: 297, 1938.

Smith, R. G.: The Present Status of Ergonovine, J. A. M. A. 111: 2201-2209, 1938.

White, A. C.: A Comparison of Some of the Ergot Alkaloids; III. General Pharmacology, Quart. J. Pharm. & Pharmacol. 17: 95, 1944.

Pituitary

Abel, J. J.: Physiological Chemical and Clinical Studies on Pituitary Principles; Harvey Society Lectures, 1923-24, Philadelphia, 1924, J. B. Lippincott Co.

Davis, M. E.: The Use and Abuse of Ergot and Pituitary, J. A. M. A. 109: 1631, 1937.

DeLee, J. B.: The Use of Solution of Posterior Pituitary in Modern Obstetrics, J. A. M. A. 115: 1320, 1940.

Geiling, E. M. K.: The Pituitary Body, Physiol. Rev. 6: 62, 1926.

Geiling, E. M. K.: The Posterior Hypophysis, Chap. X *in* Glandular Physiology and Therapy, Chicago, 1935, American Medical Association.

Kamm, O., et al.: The Active Principles of the Posterior Lobe of the Pituitary Gland, J. Am. Chem. Soc. 50: 573, 1928.

Moir, C.: The Effect of Posterior Lobe Pituitary Gland Fractions on the Intact Human Uterus, J. Obst. & Gynaec. Brit. Emp. 51: 181, 1944.

Van Dyke, A. B.: The Physiology and Pharmacology of the Pituitary Body, Chicago, 1936, The University of Chicago Press.

CHAPTER XVII

DIURETICS

Diuretics are drugs which increase the formation of urine. A large variety of substances can increase the volume of urine, for the kidney is a very complex organ and its activity may be modified in a number of different ways. The term *diuretic,* however, is reserved for those drugs which have a major action on the kidney which is applicable clinically.

Urine Formation

The pharmacology of the kidneys differs markedly from that of other glands, such as the salivary glands. Like most glands, the kidneys are supplied with nerves from the autonomic nervous system. While stimulation of these renal nerves may affect the secretion of urine, they have no direct influence on the kidney cells, the changes in renal function being due chiefly to alternation in the blood pressure; for example, atropine may stimulate circulation and consequently increase diuresis, but pilocarpine may influence urine formation by depleting the moisture of the body by stimulating sweat formation. The kidneys may function well even when their nervous mechanism is severed. There is evidence that the kidneys contain both vasoconstrictor and dilator nerves.

The Function of the Kidneys.—The kidneys are the chief organs that excrete nonvolatile substances from the body. The normal kidney is impermeable to colloids and therefore excretes none of the normal colloidal constituents of the blood. The chief functions of the kidneys are: (1) the excretion of the waste products of nitrogen metabolism, i.e., urea, uric acid, etc.; (2) the excretion of organic and inorganic constituents not needed or not metabolized by the body; (3) the maintenance of the osmotic pressure of the blood at a constant level, and the maintenance of the alkaline reserve of the blood by excretion of nonvolatile acids formed in metabolism.

Theories of Renal Function.—The exact mechanism by which urine is formed is not known. No theory is likely to be wholly correct, but the simplest theory of kidney secretion, that is in accord with a modern knowledge of physical chemistry, is the theory postulated by Cushny (1926) and further strengthened by observations of Richards, and Wearn and Richards. This theory conceives that urine is formed at the glomerulus by a process of filtration, and that during its passage through the uriniferous tubules certain elements in it are reabsorbed by a vital process on the part of the tubular epithelium into the blood system of the kidney. The renal unit is shown in Fig. 31. This process is one of selective reabsorption.

There are certain bodies in the glomerular urine known as "threshold bodies" which are necessary for the body nutrition and which have an established threshold value. These substances are found in the urine. Other substances found in the urine in the tubules are "nonthreshold bodies" and are eliminated as waste matter. The process is one of filtration in the glomerulus, and in the tubules one of selective ab-

sorption of a fluid of the same composition as normal plasma, leaving a residue called urine. The glomerular filtrate contains:

1. Nonthreshold substances, including such abnormal constituents as sodium nitrate, sodium phosphate. (Will act as diuretics in any concentration.)
2. Low threshold substances, such as urea and potassium salts, uric acid, hippuric acid, creatinine, etc.
3. High threshold substances, which are completely reabsorbed under normal conditions, e.g., glucose. (The low or high threshold substances will produce diuresis so long as their concentration in the plasma surpasses their normal threshold value.)

Mechanical Values.—

1. *Osmotic Pressure.*—Osmotic pressure affects the secretion of urine. A large increase in the urinary flow can be brought about by the intravenous injection of saline diuretics, such as sodium sulfate, potassium nitrate, or neutral crystalloids as urea or sugar. These substances, which either are not reabsorbed in the tubules or else are secreted by the tubules, raise the osmotic pressure of the fluid upon which the water-reabsorbing cells are operating and thus increase the water excreted.

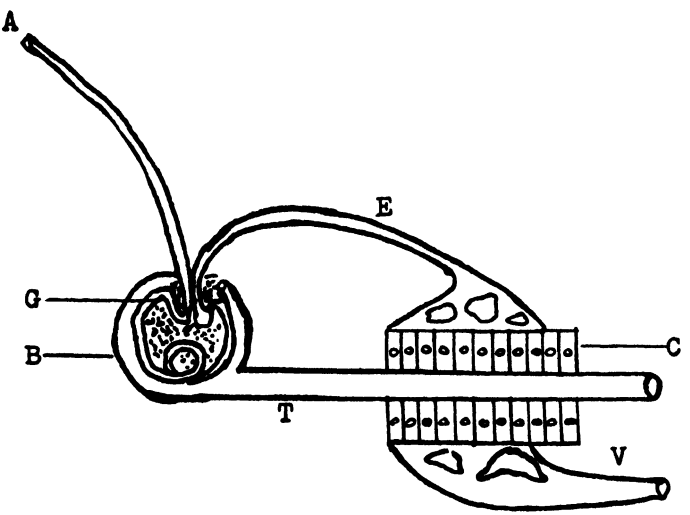


Fig. 31.—Renal unit. *A*, Afferent vessel; *B*, Bowman's capsule; *C*, cells of tubule; *E*, efferent vessel; *G*, glomerulus; *T*, tubule; *V*, efferent vein.

2. *Filtration Pressure.*—Filtration pressure, i.e., the difference between the pressure in the glomerular capillaries and in Bowman's capsule, if reduced to one-third at the entering artery in the glomerulus, is insufficient for urine filtration. A decrease in concentration of plasma protein increases filtration. Such an effect is produced by the intravenous injection of saline solution.

An increase in pressure in the glomerular capillaries may be obtained by the administration of digitalis which stimulates the heart action. A similar increase may be obtained by constriction of the efferent glomerular veins by small doses of epinephrine or pituitary.

3. *Permeability.*—The permeability of glomeruli and tubules may be altered. Irritant substances, such as cantharidin, volatile oils, and possibly calomel, may act by irritating the tubules and thus reducing their water-absorbing capacity. Certain drugs alter the permeability of the kidney. The glucoside, phloridzin, produces diuresis, and makes the kidney permeable to sugar. The threshold value of glucose is approximately 0.2 per cent, but phloridzin lowers this threshold value to zero. Atophan lowers the threshold of uric acid excretion from a normal of about 0.003 per cent to zero and causes the uric acid in the blood to be excreted.

Tables giving the percentage constituents of normal urine and plasma would show that substances like glucose or colloids are not excreted, those which are concentrated relatively little (Na, Cl, Ca, Mg), those which are moderately concentrated (uric acid, K, PO_4), and finally those which are concentrated greatly (NH_4, urea, SO_4, creatinine).

4. *Oxygen Supply.*—The kidney requires considerable oxygen for proper function, e.g., digitalis increases circulation and thus oxygen supply to the kidney. Hydrogen cyanide stops the oxidation process.

5. *Increase in Number of Functioning Renal Units.*—There are about a million renal units in each human kidney and Richards suggests that only a certain number of capillary tufts are open at once. Thus to increase kidney secretion the simplest method would be to increase the proportion of units functioning. Probably caffeine and urea cause an increase of these units.

In the light of Cushny's theory it is necessary to assume that the glomeruli filter 200 to 300 liters a day. These figures are not impossible, for the whole total surface of the glomerular membranes in the human kidneys are estimated to be over ten square meters, while the total length of the tubules is about fifty kilometers. The evidence is inconclusive whether the tubules can secrete substances as well as absorb them, but whatever the mode of action, they perform a large amount of work and require an ample oxygen supply.

Use of Diuretics.—Diuresis is theoretically desirable in a number of clinical conditions—anuria, oliguria, uremia, edema, and in toxic and infectious conditions—to eliminate poisons. The chief clinical use is to *promote the excretion of edema fluid.* Diuretics are indicated in congestive heart failure when edema and dyspnea persist after rest, digitalis in adequate dosage, and restriction of fluid and salt intake. Through diuresis the heart is relieved of the added burden of propelling the blood through the compressed blood vessels; the blood volume is decreased, and likely the efficiency of the heart is increased by loss of edema from the myocardium. Ascites due to congestive heart failure generally disappears under diuretic therapy. However, hydrothorax, on the other hand, tends to remain unchanged and removal by mechanical means is indicated.

Physiology of Edema Formation.—Edema fluid arises from the blood and results from imbalance of those forces which govern the transfer of fluid across the capillary membranes. The capillary membrane is permeable to all the constituents of the blood except serum protein, lipoids, and cellular elements. As long as the hydrostatic pressure within the capillary is greater than the osmotic pressure exerted by the serum proteins, fluid passes from the capillary into the extracellular spaces and this occurs chiefly at the arterial end. On the other hand, extracellular fluid diffuses back into that portion of the capillary where the hydrostatic pressure is less than the osmotic pressure of the serum protein—this occurs mainly at the venous end.

Three factors favor edema formation: (1) decrease in the concentration of serum protein, (2) increase in hydrostatic pressure within the capillary, and (3) injury to the capillary walls increasing their permeability to protein. In the dependent edema, so often seen in congestive heart failure, the increased hydrostatic pressure within the capillaries causes the fluid to pass into the tissues. The capillary hydrostatic pressure increases as the result of increased venous pressure, transmitted from the right heart to the venous end of the capillary.

We must remember that diuretics have a limited value in nephritis because the injured kidney usually works to the maximum of its ability and it is impossible to increase the action by drugs. The treatment of kidney disease, must, so far as is possible, be directed at decreasing the load on the kidney by appropriate diet and by calling in other forces to assist in elimination of waste products, rather than by trying to force the injured tissue to perform more work.

Prompt removal of edema from the body is conducive to the most rapid reestablishment of circulation. Many methods are used to rid the body of edema, such as paracentesis, rest in bed, the salt-free diet, restricted fluid intake, and digitalization. Other more specific measures are indicated. The use of *diuretics* is the most desirable of these special measures for the elimination of excess body fluid. The diuretic drugs most commonly used in medicine are included in the following classification.

Classification of Diuretics

I. Mercurial Diuretics
   - A. Mersalyl (Salyrgan), U.S.P.
   - B. Mersalyl and Theophylline Injection, U.S.P.
   - C. Mercurophylline Injection, U.S.P.
   - D. Meralluride Sodium Solution, N.N.R.

II. Xanthine Diuretics
   - A. Theobromine and Sodium Acetate, U.S.P.
   - B. Theobromine and Sodium Salicylate, N.F.
   - C. Theocalcin, N.N.R.
   - D. Theophylline, U.S.P.
     - Theophylline Tablets, U.S.P.
   - E. Aminophylline, U.S.P.
     - Aminophylline Injection, U.S.P.
     - Aminophylline Tablets, U.S.P.
   - F. Theophylline and Sodium Acetate, U.S.P.
     - Theophylline and Sodium Acetate Tablets, U.S.P.

III. Saline Diuretics
   - A. Potassium Salts
   - B. Acid-producing Salts

IV. Miscellaneous
   - A. Water
   - B. Urea
   - C. Glucose and Sucrose

Mercurial Diuretics

The mercurial diuretics are our most powerful and consistently effective diuretics. Calomel was used for this purpose by Paracelsus in the sixteenth century. It was an ingredient of the famous "Guy's Hospital Pill." In 1886 Jendrassik showed that the administration of

calomel in cases of cardiac edema caused marked diuresis and increased the excretion of chlorides. Calomel immediately became popular as a diuretic, but excessive diarrhea accompanied its use and it began to lose favor as a diuretic.

Mode of Action.—Mercurial diuretics act on the tubules of the kidney by interfering with the reabsorption of water and sodium chloride. The effect on the heart is secondary. The fall in venous pressure may not occur for several hours after diuresis has begun from a mercurial intravenously, whereas the pressure begins to fall in about ten minutes after injection of the mercurial and a rapidly acting glycoside such as ouabain.

The commonly used mercurial diuretics contain theophylline. The presence of this xanthine prevents necrosis of tissues at the site of injection, prevents the storage of mercury and increases the concentration of the mercurial within the kidney, thus facilitating diuretic action.

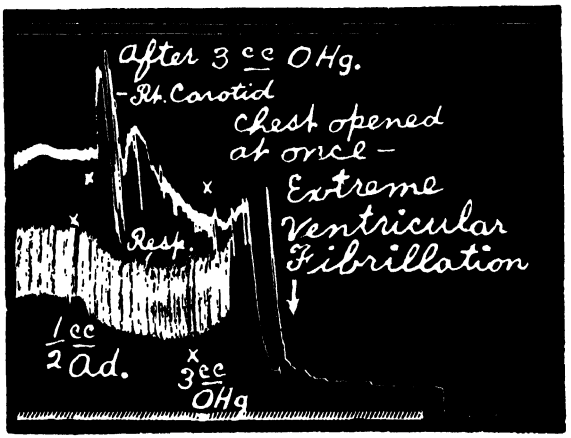


Fig. 32.—Carotid blood pressure and respiration showing the marked cardiac irregularities and final ventricular fibrillation caused by repeated doses of mersalyl (salyrgan). (From Jackson: *Experimental Pharmacology and Materia Medica.*)

Toxicity of Mercurial Compounds.—Toxic reactions to mercurial diuretics include dyspnea, substernal oppression, cyanosis, sweating, bradycardia and syncope. Mercurials in large doses affect the circulation. Fig. 32 shows that large doses of mersalyl (salyrgan) raise the blood pressure, produce marked irregularity of rhythm and finally ventricular fibrillation. Respiration is depressed. Novasurol, 30 mg. per Kg., produces marked rise of blood pressure, apparently by vasoconstriction. Repeated large doses cause cardiac irregularity and death by ventricular fibrillation (D. E. Jackson, 1926).

The effect of mersalyl (salyrgan) on kidney volume, blood pressure, and respiration is shown in Fig. 33.

Mercurial diuretics produce toxic action on the basis of *sensitivity* of the patient. This manifests itself as urticaria, rash, chills, and fever. The *depletion of sodium* caused by the diuretic action may occur with abdominal colic, muscle cramps, and nausea and vomiting. Another reaction that is often overlooked is a spontaneous *redigitalization*

due to mobilization of digitalis from edema fluid. This may be avoided by placing the patient on a smaller digitalis maintenance dose or by administering a smaller amount of diuretic. *Sudden death* does occasionally occur but such a reaction is rare. The incidence can be reduced if care is exercised in avoiding use of mercurials in hypersensitive patients and those with renal or hepatic disease.

The direct toxic effects of the mercurial diuretics are principally on the kidneys, producing tubular degeneration, and on the gastrointestinal tract, producing stomatitis and colitis; chills and fever have also been noted, and more rarely a state resembling shock. A proportion of the sudden toxic effects, including the occasional sudden deaths, may be due to the development of hypersensitiveness to the drug. The reported fatalities and toxic reactions should not discourage the rational use of mercuric diuretics. They should, however, serve as a warning and explanation of what to expect in rare instances or following promiscuous use of such agents.

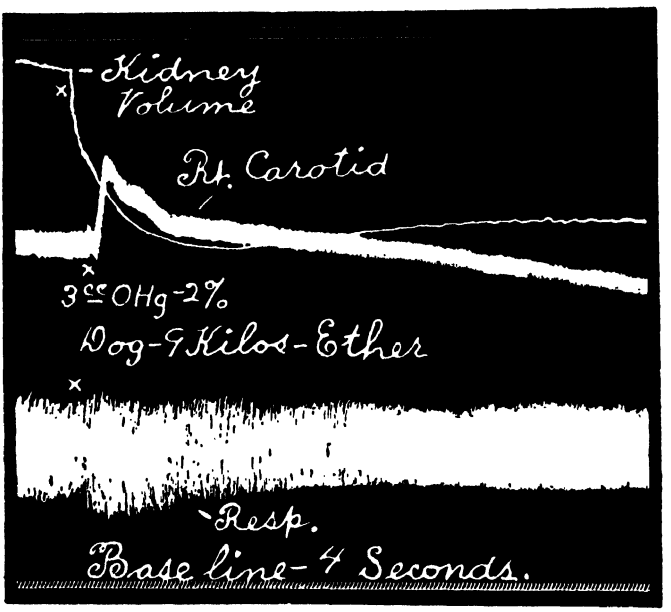
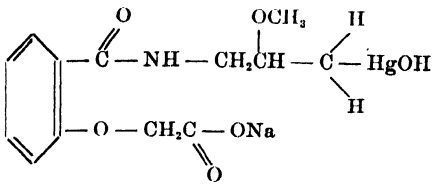
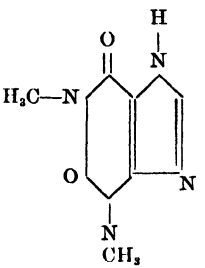


Fig. 33.—Kidney volume, blood pressure, and respiration showing the action of mersalyl (salyrgan—3 cc. of 2 per cent solution). (From Jackson: *Experimental Pharmacology and Materia Medica.*)

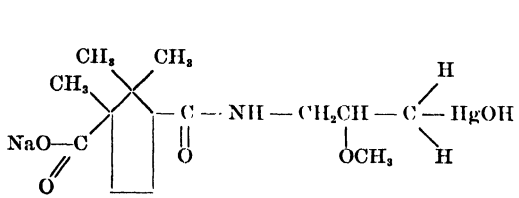
Mersalyl (Salyrgan), U.S.P.—Salyrgan is a complex organic mercurial containing 39.6 per cent mercury. It is used especially in edema or ascites of cardiac origin. Profuse diuresis may follow a single injection. It is less toxic than novasurol and only very rarely has it precipitated a toxic anuria. Salyrgan action depends on sufficient normal renal tissue and is therefore contraindicated in acute kidney diseases and advanced nephritis.

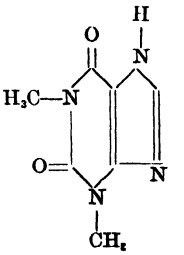
The formula for the following three commonly used mercurial derivatives are as follows:



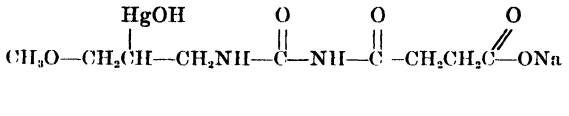


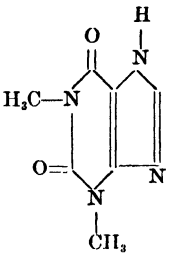
+ ¼ mol theophylline in excess
Mersalyl and theophylline





Mercurophylline





+ 1/3 mol theophylline in excess

Meralluride Sodium Solution

The mercurial diuretics containing theophylline are all about equally effective. When they are administered by vein, diuresis begins in about thirty minutes and reaches its maximum within four hours. Diuresis occurs in a large majority of the patients when the patient is fairly dehydrated. Smaller doses at more frequent intervals may be better than one large dose (2.0 cc.) once a week. The intramuscular route is preferable to intravenous.

The administration of tablets are effective in about 60 per cent of the patients. It is best to administer them after meals once or twice a day. Tablets of mersalyl and theophylline and of mercurophylline are available. Suppository administration of mercurials is effective in about 70 per cent of the patients.

Mersalyl and Theophylline Injection, U.S.P.—This preparation consists of a sterile aqueous solution of approximately 10 parts by weight

of mersalyl ($C_{13}H_{16}HgNO_6Na$) to 5 parts by weight of theophylline ($C_7H_8N_4O_2.H_2O$). It contains about 42 per cent mercury (Hg).

Mersalyl and theophylline injection has been demonstrated to produce less local reaction on intramuscular injection than mersalyl alone and to be somewhat more effective. It is believed that the more rapid resorption of mersalyl in combination with theophylline accelerates diuresis and, by preventing the deposition of mercury, improves the local tolerance. It is used as a diuretic for dropsy in cardiorenal diseases, but is contraindicated in acute nephritis and chronic kidney disease with marked tubular and glomerular changes.

Dosage.—For adults: Administer 0.5 cc. to test for susceptibility to the drug. If well tolerated the dose may be increased to 2 cc. (each cubic centimeter contains mersalyl 0.1 Gm. and theophylline 0.05 Gm.) on the following day. Usually injections administered either intramuscularly or intravenously are not given more frequently than every three or four days. After relief from dropsy recurrences can often be prevented by occasional injections. *For children:* The dose for children is proportionately less than that for adults (0.25 cc. to test susceptibility, followed by 0.5 to 1 cc. the following day).

Mercurophylline Injection, U.S.P., is an aqueous solution of the sodium salt of a complex organic mercury compound ($C_{14}H_{26}NO_6HgNa$) and theophylline in approximately molecular proportions. It contains mercury (Hg) equivalent to about 40 per cent of the labeled amount of mercurial compound.

This drug is perhaps less toxic and more active than the mercurial alone. Crawford and McDaniel (1935) indicated that it is less toxic locally if extravasated into the tissues. They also show it to be more effective than mersalyl. Other clinical evidence indicates that the presence of theophylline enhances the rate and completeness of absorption, so that the drug is effective and well tolerated either intramuscularly or intravenously. Supplementary administration of ammonium chloride tends to increase diuresis.

Mercurophylline is indicated for removing excess fluid in congestive heart failure, nephrosis, and ascites associated with cirrhosis of the liver. It is contraindicated in chronic nephritis and acute kidney disease.

Dosage.—Administer an amount equivalent to 0.1 Gm. of mercury compound and 40 mg. of theophylline. Mercurophylline injection is supplied in a concentration of 10 per cent with respect to the sodium salt. When maximum diuresis is desired in patients with massive edema, administer 275 mg. in a single dose. In severe cases, reaccumulation of dropsical edema may be controlled with 60 to 110 mg. daily. The diuretic effect may be enhanced by 5 to 7 Gm. of ammonium chloride administered orally on the preceding day.

Meralluride Sodium Solution, N.N.R.—This diuretic is a sterile aqueous solution containing approximately 119 mg. of meralluride (equimolecular quantities of mercurated allylsuccinylurea and theophylline) and 13 mg. of theophylline per cubic centimeter. One cubic centimeter of this solution contains 39 mg. of mercury and 48 mg. of theophylline.

Meralluride sodium solution is proposed for use in edema of cardiorenal disease of nephrosis, ascites of liver disease, and other conditions in which a mercury diuretic may be indicated. It is contraindicated in acute nephritis and chronic kidney disease.

It is rapidly absorbed following muscular injection. It may also be given intravenously. The usual dose of meralluride sodium solution

is from 1 to 2 cc. An initial test dose (0.5 cc. or less) should be given to detect sensitive patients who often react with symptoms such as stomatitis, gastric upset, skin reactions, and febrile reactions.

Preparations

Mersalyl, *Mersalyl,* U.S.P. Contains about 40 per cent of mercury.

Mersalyl and Theophylline Injection, *Injectio Mersalylis et Theophyllinae,* U.S.P. *Dosage:* Intramuscular, an amount equivalent to: mersalyl 0.2 Gm. (3 grains) and theophylline 0.1 Gm. (1½ grains).

Mercurophylline Injections, *Injectio Mercurophyllinae,* U.S.P. *Dosage:* Intramuscular, an amount equivalent to: the mercury compound 0.1 Gm. (1½ grains) and theophylline, 40 mg. (⅔ grain).

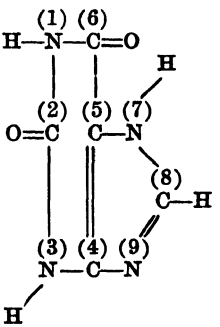
Meralluride Sodium Solution, N.N.R. *Dosage:* 1-2 cc.

Xanthine Diuretics

Von Schroeder, in 1887, demonstrated that caffeine with sodium benzoate increased both the volume and the solid constituents of urine. Richards and Plant (1915) and Cushny showed with rabbits that caffeine could produce a diuresis at times when the renal blood flow was not increased. Richards observed that caffeine caused an increased capillary flow in the glomeruli of the frog which probably meant an increased capillary permeability.

Caffeine, theobromine, and theophylline are formed by the introduction of methyl radicals into a corresponding number of NH_2 groups of xanthine. These groups occupy various positions in the xanthine (2, 6 dioxypurine) nucleus, consequently many methyl xanthines occur naturally, and several have been prepared synthetically.

The general formula for xanthine (2, 6, dioxypurine)



The following xanthines are of therapeutic importance:

1. Caffeine	1-3-7	Trimethylxanthine.
2. Theobromine	3-7	Dimethylxanthine.
3. Theophylline	1-3	Dimethylxanthine.

Action and Uses.—The xanthines are of value therapeutically for their *diuretic action* and for use as *myocardial stimulants.* Theobromine and theophylline surpass caffeine in their diuretic, and perhaps in cardiac and muscular action. They are, therefore, generally preferred in cardiac edema, etc. Theophylline surpasses theobromine in diuretic efficacy, but its action is not so lasting; its action may produce gastric upset and occasionally renal irritation. Theobromine

is, therefore, generally preferred, sometimes preceded for a few days by theophylline. Caffeine is indicated if central stimulation is desired.

The xanthines alone are rarely used today as diuretic agents except in cases in which the mercurial diuretics are contraindicated. Diuresis is not nearly as complete as when the mercurials are used.

TABLE XXV

RELATIVE ACTIONS OF XANTHINES

DRUG	DIURESIS	CORONARY DILATATION	CARDIAC STIMULATION	C.N.S. STIMULATION	RESPIRATORY STIMULATION	SKELETAL MUSCLE STIMULATION
Caffeine	3	3	3	1	1	2
Theobromine	2	2	2	3	3	1
Theophylline	1*	1	1	2	2	3

*1 most potent.

Mode of Action of Xanthine Diuretics.—The mechanism of action may be vasodilatation accompanied by cardiac stimulation. The action may be increased due to the xanthines causing an increased permeability of the glomeruli. These compounds may also increase the number of glomeruli actively functioning. In order to produce diuresis with these compounds there must be a positive water balance. In fever (mild dehydration) no diuresis occurs.

Cushny and Lambie (1921) observed that the diuretic action of caffeine far outlasted the vasodilation of the renal vessels. From this observation they postulated that the permeability of the glomerular capsule must be increased and thus glomerular filtration enhanced. Others claim that the affinity of serum proteins for water is reduced, and evidence has also been reported to show a mobilization of fluid into the blood under the influence of the xanthines.

Xanthine derivatives of clinical importance include:

Theobromine and Sodium Acetate, U.S.P.—A hydrated double salt of theobromine sodium and sodium acetate ($NaC_7H_7O_2N_4 + NaC_2H_3O_2$), containing approximately 60 per cent of theobromine. It acts like theobromine but has the advantage of greater solubility and of being well tolerated by the stomach. It is inferior in diuretic power to theophylline but is said to have more prolonged diuretic action. *Dosage:* Administer 0.5 to 1 Gm., preferably in capsules. If in solution administer in peppermint water.

Theobromine and Sodium Salicylate, N.F., contains sodium theobromine and sodium salicylate in approximately molecular proportions. It contains not less than 46.5 per cent of theobromine and not less than 35 per cent of salicylic acid. It is a soluble salt with much the same action as caffeine, except that it has no stimulating effect on the central nervous system. Its action and uses are practically identical with those of theobromine and sodium acetate. *Dosage:* 1 Gm. (15 grains).

Theocalcin, N.N.R., is a double salt or mixture of calcium theobromine ($[C_7H_7O_2N_4]_2Ca$) and calcium salicylate ($[C_7H_5O_3]_2Ca$). It contains not less than 44 per cent of theobromine.

Theocalcin acts like theobromine, but is more soluble. It has a saline taste and is only partially soluble in water. Administer orally. *Dosage:* Administer from 0.5 to 1 Gm. three times a day.

Theophylline, U.S.P.—Theophylline is an isomer of theobromine or 1-3, dimethylxanthine. It is slightly soluble in water (1:120). It is

prepared synthetically. Theophylline has a diuretic action similar to that of theobromine but is more powerful and is said to be not so lasting. It is indicated in *angina pectoris* and *edema of cardiac origin.* *Dosage:* Capsules or tablets, 0.20 Gm. three times daily.

It may cause nausea, vomiting, and diarrhea. Care must be exercised in the use of this drug, as it exerts a strong stimulating action on the central nervous system, and in several instances it has caused convulsions.

Aminophylline, U.S.P., or theophylline ethylenediamine, is a combination of theophylline and ethylenediamine. It contains 75 to 82 per cent anhydrous theophylline ($C_7H_8O_2N_4$) and approximately 13 per cent ethylenediamine $C_2H_4(NH_2)_2$. It is soluble in water 1:5.

Aminophylline possesses similar action and uses to theophylline and theophylline and sodium acetate, but is more soluble. Used intravenously, aminophylline is effective in relieving the paroxysmal dyspnea or pulmonary edema of cardiac origin. The xanthines present stimulate the heart muscle. Some claim there is an increased coronary flow, but this has not been satisfactorily substantiated.

Aminophylline is effective in the treatment of *bronchial asthma,* especially that not relieved by epinephrine.

As a diuretic the drug is given in doses of 0.1 to 0.2 Gm. three times a day orally, if indicated. Smaller doses are preferred in most cases. Aminophylline may be administered in the form of rectal suppositories or as a retention enema. The intramuscular dose is 0.48 Gm. The intravenous dose is 0.24 to 0.48 Gm. to be given slowly (N.N.R.).

Theophylline and Sodium Acetate, U.S.P.—This preparation contains between 55 and 65 per cent of anhydrous theophylline ($C_7H_8O_2N_4$). It is soluble in water (1:25). Its action is similar to theophylline but it has the advantage of being more soluble.

Administration.—Theophylline and sodium acetate is a valuable diuretic. Doses of 0.2 Gm. (3 grains) every three hours, four times a day, should produce good diuresis.

Preparations

Theobromine and Sodium Acetate, *Theobromina et Sodii Acetas,* U.S.P. *Dosage:* 0.5 Gm. (7½ grains).

Theobromine and Sodium Acetate Capsules, *Capsulae Theobrominae et Sodii Acetatis,* U.S.P. *Dosage:* 0.5 Gm. (7½ grains) theobromine and sodium acetate.

Theobromine and Sodium Salicylate, *Theobromina et Sodii Salicylate,* N.F. *Dosage:* 1 Gm. (15 grains).

Theophylline, *Theophyllina,* U.S.P. *Dosage:* 0.2 Gm. (3 grains).

Theophylline Tablets, *Tabellae Theophyllinae,* U.S.P. The usual sizes contain 0.1 Gm. and 0.2 Gm.

Aminophylline, *Aminophyllina,* U.S.P. (Theophylline Ethylenediamine, U.S.P. XII). *Dosage:* 0.2 Gm. (3 grains).

Aminophylline Injection, *Injectio Aminophyllinae,* U.S.P. (Theophylline Ethylenediamine Injection, U.S.P. XII). *Dosage:* Intramuscular or intravenous 0.1 Gm. of aminophylline.

Aminophylline Tablets, *Tabellae Aminophyllinae,* U.S.P. (Theophylline Ethylenediamine Tablets, U.S.P. XII). Usual sizes contain 0.1 Gm. and 0.2 Gm.

Theophylline and Sodium Acetate, *Theophyllina et Sodii Acetas,* U.S.P., B.P. *Dosage:* 0.2 Gm. (3 grains).

Theophylline and Sodium Acetate Tablets, *Tabellae Theophyllinae et Sodii Acetatis,* U.S.P. Usual sizes contain 0.1 Gm. and 0.2 Gm.

Saline Diuretics

The volume of urine is increased by all salts that are excreted by the kidneys. The "saline" diuretics may well include those substances which act by *salt action.* Such substances include nontoxic salt solutions, urea, glucose, etc.

Mode of Action.—Saline diuretics raise the filtration pressure by increasing the total quantity of fluid, and by lowering the viscosity, thereby reducing friction in the arterioles and capillaries. The increase in fluid diminishes the water affinity of the colloids. Some of the saline diuretics may act by stimulating the secretory cells or by depressing reabsorption by the tubules.

For convenience the "saline" diuretics may be divided as follows: potassium salts and acid-producing salts. The saline diuretics are frequently used to enhance mercurial diuresis. The administration of 3 Gm. of ammonium chloride for two or three days before the mercurial diuretic is given may increase diuresis as much as 20 per cent. Potassium chloride and ammonium nitrate will also enhance diuresis.

Potassium Salts.—Certain potassium salts (KCl, KNO_3, $KHCO_3$) have been used as diuretics in clinical medicine for many years. Wilks and Taylor (1863), and more recently Barker (1932), and Keith and Binger (1935) used potassium salts with considerable success. Keith (1925-1935) showed that following the administration of potassium salts the kidney was able to concentrate the potassium delivered to it by the blood serum approximately fifty times. Lack of absorption by the renal tubules is the most plausible explanation of this concentration of potassium. Potassium nitrate caused a relatively greater diuresis and greater increase in the excretion of chloride and sodium than did any of the other salts.

Administration.—The usual initial daily dose of potassium chloride is 9 grams, and that for the nitrate and the bicarbonate is 12 grams. Administration of the chloride or the nitrate in doses of 0.5 gram, in the form of an enteric coated pill, is advised. The use of potassium salts is contraindicated in extreme cases of oliguria, or when the value for urea is greater than 100 mg. per 100 cc. of blood.

Acid-Producing Salts.—The diuretic action of acid-producing salts depends on the administration of large doses and on the liberation of the acid radical within the body. The common salts possessing diuretic properties include calcium chloride, ammonium chloride, and ammonium nitrate.

The diuretic action of acid-producing salts is thought to be caused by the shift in the acid-base equilibrium to the acid side, and the specific effect of the individual acid radical. The nitrate radical has possibly the most marked diuretic effect, while the chloride radical produces the most marked shift in the acid-base balance toward the acid side. Experience has shown that the administration of acid-producing salts preliminary to the use of mercurials is an excellent method of producing effective diuresis.

Administration.—The daily doses recommended for diuretic purposes are as follows: calcium chloride, 10 grams; ammonium chloride, 9 grams; ammonium nitrate, 12 grams. Administration of 0.5 gram doses in enteric coated pills is recommended. When administering the chloride, the possibility of acidosis must be kept constantly in mind. Methemoglobinemia may develop after the use of ammonium nitrate. A temporary renal insufficiency may occur. The use of these salts is contraindicated when the value of urea is 75 mg. or more per 100 cc. of blood.

For production of diuresis:

℞

Ammonium Chloride	30.00 Gm.	(ʒj)
Anise Water	30.00 cc.	(fʒj)
Glycyrrhizae Syrup ——q.s. ad	120.00 cc.	(fʒiv)

M. Sig.: One or more teaspoonfuls as directed.

Miscellaneous Diuretics

Water.—Water is a true physiological diuretic. Its mode of action is not definitely known. Evidence seems to indicate that the posterior pituitary is a gland of internal secretion which regulates the excretion of water in mammals. In the absence of the posterior pituitary, marked disturbances in water metabolism result. This glandular principle may control the water-reabsorbing activity of the tubules (Smith, 1937). Thus after ingestion of water, posterior pituitary activity decreases, the concentration of the antidiuretic hormone in the blood falls, tubular reabsorption of water decreases, and diuresis results. It seems quite apparent that *decreased tubular reabsorption is the basis of water diuresis.*

Although water is seldom considered a diuretic drug, the forcing of fluids is a recognized therapeutic measure. In edema, obviously water administration is contraindicated as a therapeutic measure, as it would further increase the formation of edema fluid.

Urea.—Urea, $CO(NH_2)_2$, is an effective diuretic, acting probably by simple osmosis. The drug is soluble in water (1:1) and in alcohol (1:5). It exists in colorless, transparent, and almost odorless crystals. It has few, if any, toxic properties.

Urea in doses of 20 to 60 Gm. (⅔ to 2 ounces) is a useful diuretic. It acts as a nonthreshold substance, taking water with it when excreted by the kidney. It is frequently used with the mercurial diuretics.

Urea is not a widely used diuretic. Hyman (1936) reports its use in alternate periods of three to five days of administration and omission, with excellent diuresis in 83 per cent of the cases and no toxic effects. The drug has an objectionable taste and, of course, is contraindicated in patients already retaining nitrogen. The following prescription is given us by Beckman:

℞

Urea	30.00 Gm.	(ʒj)
Acacia	12.00 Gm.	(ʒiij)
Cinnamon Syrup ——q.s. ad	120.00 cc.	(fʒiv)

M. Sig.: One or more teaspoonfuls well diluted.

Glucose and Sucrose.—Glucose and sucrose are commonly used diuretics. Glucose must be given in sufficient amounts to exceed the renal threshold for this substance. The glucose not reabsorbed in the proximal tubule of the kidney exerts an osmotic effect in the loop of Henle and thus produces diuresis. Glucose must be given intravenously in large doses and in high concentration to be effective. The usual dose is 50 cc. of 50 per cent solution.

Sucrose may be even more effective than glucose. Although the sucrose molecule is twice as large as the glucose molecule, and therefore exerts one-half the osmotic effect of glucose, nevertheless, it cannot be metabolized when administered by vein and thus circulates as a foreign substance until excreted by the kidney. Of importance too is the fact

that tubular reabsorption of sucrose is negligible. The usual dose is 100 cc. of 50 per cent solution.

Other drugs, such as digitalis, thyroid, and parathyroid, possess diuretic action but they are not primarily diuretic drugs.

Preparations

Ammonium Chloride, *Ammonii Chloridum*, U.S.P. *Dosage:* For diuresis from 3 to 6 Gm. (45 to 90 grains) daily, care being taken to avoid excessive acidosis. B.P., 0.3-4 Gm. (5-60 grains).

Ammonium Chloride Capsules, *Capsulae Ammonii Chloridi*, U.S.P. Usual sizes contain 0.3 Gm. or 0.5 Gm.

Calcium Chloride, *Calcii Chloridum*, U.S.P., B.P. *Dosage:* 1 Gm. (15 grains) in solution.

Potassium Chloride, *Potassii Chloridum*, U.S.P. *Dosage:* 1 Gm. (15 grains).

Potassium Chloride Tablets, *Tabellae Potassii Chloridi*, U.S.P. Usual sizes contain 0.3 and 0.5 Gm.

Potassium Nitrate, *Potassii Nitras*, N.F. (Saltpeter). *Dosage:* 1 Gm. (15 grains). B.P., 5-15 grains.

Potassium Acetate, *Potassii Acetas*, U.S.P., CH_3COOK. *Dosage:* 1 Gm. (15 grains). B.P., 1-4 Gm. (15-60 grains).

Sodium Sulfate, *Sodii Sulfas*, U.S.P. (Glauber's Salt). *Dosage:* 15 Gm. (4 drachms). B.P., 2-16 Gm. (30-240 grains).

Urea, *Urea*, U.S.P., B.P. (Carbamide). *Dosage:* 8 Gm. (2 drachms).

Use of Diuretics to Control Edema in Heart Disease

The most effective diuretics are probably the mercurials which produce diuresis through interfering with reabsorption of fluid by the renal tubules. Mercurophylline injection, mersalyl and theophylline injection, or meralluride sodium solution may be used. They are usually given intravenously in doses of 1 to 2 cc. once or twice a week. The muscular route is probably as effective and is safer.

When parenteral therapy is contraindicated, mercurophylline may be administered orally or rectally, but the results are not quite as effective.

The xanthine diuretics are less effective than the mercurials, but excellent results often occur. Theobromine and sodium acetate or aminophylline may be given in doses of 0.2 Gm. three times a day.

The saline diuretics may be given, such as ammonium chloride or ammonium nitrate in doses of 2 Gm. three times a day. Potassium chloride, 5 Gm. a day, may be given in divided doses. Urea may also be tried in a dose of 10 to 50 Gm. daily, well diluted. In persistent cases of edema, diuretics may be given for many months with little fear of kidney damage, if blood urea concentration is normal.

References

Beiter, R. N., and Wright, H. N.: The Kidneys in Health and Disease, Philadelphia, 1935, Lea and Febiger, pp. 701-708.

Berglund, H., and Medes, G.: The Kidney in Health and Disease, Philadelphia, 1935, Lea and Febiger.

Cantarow, Abraham, and Trumper, Max: Clinical Biochemistry, ed. 3, Philadelphia, 1945, W. B. Saunders Co.

Clark, A. J.: Applied Pharmacology, ed. 6, Philadelphia, 1938, The Blakiston Co.

Cushny: The Secretion of Urine, London, 1926, Longmans Green and Co.

De Graff, A. C.: Diuretics, J. A. M. A. 136: 1025, 1948.
Keith, N. M.: The Actions and Uses of Diuretics, J. A. M. A. 107: 2047, 1936.
Marshall, E. K., Jr.: The Comparative Physiology of the Kidney in Relation to Theories of Renal Function, Physiol. Rev. 14: 133, 1934.
Richards, A. N.: Harvey Lectures 16: 163, 1920-1921.
Smith, H. W.: The Physiology of the Kidney, New York, 1937, Oxford University Press.

Mercurial Diuretics

Barker, M. H., Lindberg, H. A., and Thomas, M. E.: Sudden Death and Mercurial Diuretics, J. A. M. A. 119: 1001, 1942.
Batterman, R. C., De Graff, A. C., and McCormack, J. E.: The Effectiveness and Safety of Mercupurin Administered Orally in the Treatment of Congestive Heart Failure, J. A. M. A. 124: 1243, 1944.
Keith, N. M., and Johnstone, B. I.: The Action of Merbaphen (Novasurol) on the Kidney of the Dog; a Combined Functional and Pathologic Study, Arch. Int. Med. 44: 438-454, 1929.
Keith, N. M., and Whelan, Mary: A Study of the Action of Ammonium Chloride and Organic Mercury Compounds, J. Clin. Investigation 3: 149-202, 1926.
Maxwell, E. S., Scott, J. W., and Harvey, John: A Study of the Effect of Mercurial Diuretics on Kidney Disease, J. A. M. A. 101: 2074, 1933.
Modell, W.: The Optimal Dose of Mercurial Diuretics, Ann. Int. Med. 20: 265, 1944.
Ruskin, A., and Herrmann, G. R.: Studies in Combined Diuretic Therapy, J. Lab. & Clin. Med. 29: 486, 1944.
Wexler, J., and Ellis, L. B.: Toxic Reactions to the Intravenous Injection of Mercurial Diuretics, Am. Heart J. 27: 86, 1944.

Xanthine Diuretics

Curtis, G. M.: The Action of the Specific Diuretics, J. A. M. A. 93: 2016-2018, 1929.
Schmitz, H. L.: Studies on the Action of Diuretics: I. The Effect of Euphylline and Salyrgan upon Glomerular Filtration and Tubular Reabsorption, J. Clin. Investigation 11: 1075-1097, 1932.
Walker, A. M., Schmidt, C. F., Elsom, K. A., and Johnston, C. G.: The Effect of Pituitrin, Water, Theophylline and Salyrgan on the Renal Blood Flow and Creatinine Clearance in Unanesthetized Rabbits and Dogs, J. Pharmacol. & Exper. Therap. 57: 146, 1936.

Saline and Miscellaneous Diuretics

Barker, M. H.: Edema as Influenced by a Low Ratio of Sodium to Potassium Intake, Clinical Observations, J. A. M. A. 98: 2193-2197, 1932.
Hayman, J. M., Jr.: The Clinical Use of Diuretics, J. A. M. A. 107: 1937, 1936.
Keith, N. M., and Binger, M. W.: Diuretic Action of Potassium Salts, J. A. M. A. 105: 1584-1590, 1935.
Keith, N. M., Whelan, Mary, and Bannick, E. G.: The Action and Excretion of Nitrates, Arch. Int. Med. 46: 797-832, 1930.

CHAPTER XVIII

BIOLOGICALS

I. VITAMINS

> "For it is now clear to anyone who will study the evidence, that nutrition has greater constructive potentiality than science had foreseen, and that even in the everyday choice of food we are dealing with values which are above price, for the health and efficiency, duration and dignity, of human life."
>
> —Henry C. Sherman.

The following definition for vitamins is commonly given: *Vitamins are accessory organic substances which exist in small quantities in foods, produce no energy themselves, but influence nutrition by regulating metabolic processes in cells by virtue of their specific molecular structure.*

Since vitamins are indispensable constituents of the diet, and since disease produced by their absence can be cured by their administration, they may be considered therapeutic agents.

We should recognize that there is nothing mysterious or magic about vitamins. They are necessary compounds which the body itself cannot synthesize. There is no essential difference, for instance, between the amino acids and the vitamins. It is as important to have an adequate supply of the indispensable amino acids as to have the required quantity of the various vitamins. To secure the proper intake of amino acids one selects a diet rich in proteins containing the various amino acids. Likewise, in order to prevent vitamin deficiency, the logical course is to select natural foods that are rich in the various vitamins. It is well to bear in mind that a diet which is well balanced and contains sufficient calories will, as a rule, be found to contain adequate amounts of the several vitamins necessary for adults. Foods such as fruits, tomatoes, carrots, cabbage, milk, butter, eggs, liver, whole wheat flour, and fish are all rich in vitamins. On the other hand, white flour, sugar, lard, and syrup contain little or no vitamins.

At present there are twenty or more naturally occurring compounds having vitamin activity which have been isolated and identified. Several others have been postulated. Although they act essentially as catalysts in the complex chemical processes of life, daily replenishment is needed not only during growth, but throughout life. The partial lack of any one of them interferes with bodily health, more severe deficiency causes anatomical changes, and total lack in time causes death.

It is becoming more fully recognized that mild and latent forms of vitamin deficiencies are common in medical practice. Recently the most striking signs and symptoms of some deficiency syndromes have been shown to be specifically related to some one vitamin, but it must be emphasized that, in man, there is always more than one deficit, that foods are complex and that total diets are even more complex. Furthermore, there are relationships between all nutrients during digestion and absorption and metabolism so that a lack of one or another essential substance may interfere with the proper utilization of others.

The normal alimentary tract absorbs all vitamins. Mineral fats interfere with the absorption of fat-soluble vitamins, especially A and carotene. Bile is essential for the absorption of vitamin K. The skin

probably does not absorb the water-soluble vitamins B and C, but it absorbs the fat-soluble vitamins A, D, and K in sufficient amounts to have curative effects.

The *mode of action* of vitamins is not fully understood. Their action is generally that of coenzymes, the simple parts of special enzyme systems.

It is a good practice to depend on the proper foods for vitamins. It is cheaper and furthermore it is very probable that many vitamins yet undiscovered may be essential for our bodily health, and the only sure way of getting these substances is in natural foods. Since the average American diet is low in vitamins A, D, and also in vitamins of the B complex, it is highly important to fortify our dietary with these vitamins.

The usual causes of an insufficient supply of vitamins are:

1. *Decreased intake* due to fashions, fads, special diets, diabetes, and poverty.
2. *Decreased absorption, distribution, or use,* due to gastrointestinal diseases, sprue, colitis, diarrhea, liver disease, cardiovascular disease.
3. *Increased needs,* as during growth, pregnancy, lactation, exercise, fever, and other causes.
4. *Increased loss,* as during diarrhea, polyuria, and sweating.

Vitamins are not stimulants and will not cure that "tired feeling" unless the patient actually suffers from avitaminosis. *There is no known antirheumatic vitamin.* There is no satisfactory evidence that vitamins improve the output of factory workers. It has not been clearly shown that any vitamin has any relationship to rheumatic disease. It is true that deficiency of certain vitamins exists not infrequently in patients with arthritis; in such cases vitamin therapy will indirectly benefit the arthritis. Vitamins in such cases are part of the treatment for general health and not a "specific" treatment for rheumatic disease. *There is no convincing evidence that vitamins increase resistance against infection* in any individual receiving an adequate diet. The effect of vitamins on immunity is still purely speculative.

Indiscriminate use of vitamins should be discouraged as our knowledge of these substances is not complete. An excess of one vitamin may tend to an increased requirement of another. Excessive vitamin intake appears capable of increasing the virulence of certain virus infections. There is also evidence to indicate that certain diseases not only are caused by vitamins, but, on the other hand, other diseases may be encouraged by certain vitamins.

In disease, the administration of concentrated vitamins is often indicated. In gastrointestinal disturbances the absorption may be so impaired that only a small percentage of the vitamin intake is absorbed. Frequently the diet is modified so that the intake of vitamins is inadequate. In certain diseases the destruction and consumption of vitamins may exceed the intake. Often lack of appetite leads to vitamin B_1 deficiency, which in turn causes further anorexia and loss of appetite.

Early symptoms of vitamin deficiency are the neurasthenic symptoms: asthenia, depression, irritability, and apprehension. The symptoms vary with the deficiency and are possibly due more to the psychological make-up. Often symptoms are precipitated by some illness or infection, overwork, or pregnancy. Often the diet which has been just sufficient for normal living fails when the body demands extra vitamins. The presenting symptoms are usually not specific or diagnostic of the

TABLE XXVI

RECOMMENDED DAILY ALLOWANCES FOR SPECIFIC NUTRIENTS*

Committee on Food and Nutrition, National Research Council, May, 1941

	CALORIES	PROTEIN (GM.)	CALCIUM (GM.)	IRON (MG.)	VITAMIN A† (I.U.)	THIAMINE (B_1) (MG.)‡	RIBOFLAVIN (MG.)	NIACIN	ASCORBIC ACID (MG.)‡	VITAMIN D (I.U.)
Man (70 Kg.)										
Moderately active	3,000	70	0.8	12	5,000	1.8	2.7	18	75	¶
Very active	4,500					2.3	3.3	23		
Sedentary	2,500					1.5	2.2	15		
Woman (56 Kg.)										
Moderately active	2,500	60	0.8	12	5,000	1.5	2.2	15	70	¶
Very active	3,000					1.8	2.7	18		
Sedentary	2,100					1.2	1.8	12		
Pregnancy (latter half)	2,500	85	1.5	15	6,000	1.8	2.5	18	100	400-800
Lactation	3,000	100	2.0	15	8,000	2.3	3.0	23	150	400-800
Children up to 12 years:										
Under 1 year§	100/kg.	3-4/kg.	1.0	6	1,500	0.4	0.6	4	30	400-800
1-3 years‖	1,200	40	1.0	7	2,000	0.6	0.9	6	35	¶
4-6 years	1,600	50	1.0	8	2,500	0.8	1.2	8	50	
7-9 years	2,000	60	1.0	10	3,500	1.0	1.5	10	60	
10-12 years	2,500	70	1.0	12	4,500	1.2	1.8	12	75	
Children over 12 years:										
Girls, 13-15 years	2,800	80	1.3	15	5,000	1.4	2.0	14	80	¶
Girls, 16-20 years	2,400	75	1.0	15	5,000	1.2	1.8	12	80	
Boys, 13-15 years	3,200	85	1.4	15	5,000	1.6	2.4	16	90	¶
Boys, 16-20 years	3,800	100	1.4	15	6,000	2.0	3.0	20	100	

*Tentative goal toward which to aim in planning practical dietaries; can be met by a good diet of natural foods. Such a diet will also provide other minerals and vitamins, the requirements for which are less well known.

†Requirements may be less if provided as vitamin A; greater if provided chiefly as the provitamin carotene.

‡One mg. of thiamine equals 333 I. U.; 1 mg. of ascorbic acid equals 20 I. U.

§Needs of infants increase from month to month. The amounts given are for approximately 6 to 8 months. The amounts of protein and calcium needed are less if derived from breast milk.

‖Allowances are based on needs for the middle year in each group (as 2, 5, 8, etc.) and for moderate activity.

¶Vitamin D is undoubtedly necessary for older children and adults. When not available from sunshine, it should be provided probably up to the minimum amounts recommended for infants.

nutritional deficiency. An evaluation of the diet is often the only practical diagnostic method available to the physician for detecting vitamin deficiency.

Daily Vitamin Needs

Daily needs are really rough estimates of what a normal person in good health actually uses. Allowances recommended by the Committee on Food and Nutrition of the National Research Council in May, 1941, are shown in Table XXVI. The allowances for thiamine, riboflavin, and niacin (nicotinic acid) are proportional to the caloric intake. This relationship has been established for thiamine and has been assumed for riboflavin and niacin because they, like thiamine, form part of the enzyme systems involved in the metabolism of carbohydrates. The following recommendations are given:

Thiamine	50- 70 micrograms per 100 calories
Riboflavin	70-100 micrograms per 100 calories
Niacin	500-800 micrograms per 100 calories

General Rules of Vitamin Therapy

1. The daily therapeutic dose of vitamins should be at least five times the maintenance requirements.

2. Since vitamins may be administered in amounts many times the maintenance requirements without toxic effects, it is better to be on the safe side and give too much rather than too little.

3. Oral administration is the method of choice. If the oral route is contraindicated, hypodermic or intramuscular injection is preferred when suitable preparations are available. Intravenous administration is effective but wasteful, as large quantities are lost in the urine.

Vitamins of special interest to the medical profession are marked (*). The others may be lacking in the diet but as yet have not been definitely connected with any specific deficiency symptoms in the human being.

Table XXVII

Water-Soluble Vitamins
Vitamin B Complex
*Thiamine (Vitamin B_1)
*Riboflavin (Vitamin B_2 or G)
*Nicotinic Acid or Nicotinic Acid Amide (Niacin or Niacin Amide)
Pyridoxine (Vitamin B_6)
Pantothenic Acid (Filtrate Factor)
Choline
Biotin (Vitamin H)
Inositol
Para-aminobenzoic Acid
Folic acid
*Ascorbic Acid (Vitamin C)
Citrin (Vitamin P)
Fat-Soluble Vitamins
*Vitamin A and Carotene
*Vitamin D or Activated Ergosterol
Alpha-Tocopherol (Vitamin E)
*Methyl Naphthoquinone (Vitamin K)

WATER-SOLUBLE VITAMINS

Vitamin B Complex

The term "Vitamin B Complex" is applied to a group of substances which have been shown to be constituents of what was formerly called vitamin B. So far, ten members of the B complex have been described and a pure compound has been associated with each vitamin.

Mode of Action.—Little is known of the action of the B complex vitamins. As you know, the activities of the body cells depend on energy changes; the most important changes are associated with oxidation-reduction reactions. The cells contain pairs of substances which form oxidation-reduction systems which form series through which atoms are transferred from the foodstuff molecule to molecular oxygen. Recently it has been shown that some of these substances in the oxidation-reduction systems are members of the B complex. For example, the yellow enzyme of Warburg and Christian found to participate in the oxidation of hexoses is a combination of *riboflavin phosphate* and a protein. The various coenzymes involved in similar oxidations were found to be phospho-pyridine nucleotides, in which the structure of nicotinic acid is found. The oxidation of carbohydrates also involves the action of carboxylase. It has beeen shown that the associated coenzyme that used to be called co-carboxylase is *thiamine diphosphate.* These examples show how closely certain members of the B complex are knit into the fundamental cellular processes.

Symptoms of Vitamin B Complex Deficiency.—Vague malaise, weakness, lassitude, nervous irritability, mild depression, muscle pains, gastrointestinal symptoms, and anorexia are early symptoms of all group B deficiencies. Later, physical signs develop in fairly definite patterns. All symptoms and signs resulting from dysfunction or degenerative changes of the peripheral nerves and heart are attributed to *thiamine* deficiency. *Nicotinic acid* deficiency seems associated with certain dermatoses and lesions of the mucous membranes and symptoms referable to the cerebral cortex and midbrain. *Riboflavin* deficiency is associated with other changes in the skin and mucosae and a variety of disorders of the visual apparatus. In addition, there are certain ocular disturbances and dermatoses which respond only to all the vitamins of the B complex.

Vitamin B Complex Therapy.—Recent findings indicate that the factor of balance of the vitamin B factors in the diet may be of importance. Only for patients with specific clinical deficiencies are the specific vitamins indicated. In such cases they are always given in addition to the whole complex. In cases with severe symptoms large doses are advised for short periods because prompt treatment is imperative (Joliffe, 1941). Since B vitamins are easily destroyed in the gut if gastric acidity is low, and since they are readily excreted in the urine, sweat and diarrheal stools, repeated and large doses (5 to 10 times normal needs) are necessary (Spies et al., 1940). The other vitamin B factors may be essential; however, if thiamine, riboflavin, and niacin are present in sufficient amounts in natural foods, the other members of the B complex may be considered adequate.

In any illness in which food cannot be given adequately, the vitamin B complex should be given to avoid the development of a deficiency state.

Natural Sources of B Complex Vitamins.—As the basis of all therapy with B vitamins, one of the natural sources known to contain all the members of this group should be chosen. Wheat germ, liver, and yeast are three such sources.

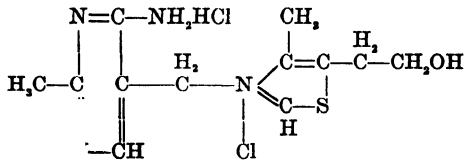
WHEAT GERM.—Wheat germ is an excellent source of the natural form, not concentrated. It is usually standardized. Wheat "middlings" is another valuable and economical source of the B vitamins.

LIVER.—Liver concentrates and extracts are made especially to supply the antipernicious anemia factor. Much of the thiamine and other factors are lost and must be provided for. The crudest form is richest in vitamins and poorest in antipernicious anemia factor. Many preparations on the market contain extra crystalline vitamin B factors.

YEAST.—Brewer's yeast contains all of the known B factors, namely, thiamine, riboflavin, niacin (nicotinic acid), pyridoxine, pantothenic acid, inositol, biotin, para-aminobenzoic acid, choline, as well as others not isolated. Yeast provides an excellent form for the treatment of vitamin B deficiencies. It is available in powdered and paste forms, as well as in compressed tablets.

Thiamine (Vitamin B_1)

Thiamine or vitamin B_1 was first isolated in crystalline form in 1926 by Jensen and Donath, and its empirical formula was determined by Windom in 1932. It was synthesized and its structural formula determined by Williams in 1936. Thiamine hydrochloride is a white crystalline substance readily soluble in water and possessing a salty nutlike flavor. The empiric formula is $C_{12}H_{18}N_4OSCl_2$, and the structural formula is as follows:



Thiamine Hydrochloride (Vitamin B_1)

In the dry state, thiamine hydrochloride is stable, and heating at 100° C. for twenty-four hours does not diminish its potency. In aqueous solutions (at pH 3.5) it can be sterilized at 120° C. for twenty minutes. It is rapidly destroyed in neutral or alkaline solutions. This vitamin also seems to be very rapidly destroyed in dehydrated meats and vegetables when the moisture content is approximately 5 per cent.

Thiamine is readily *absorbed* from the gastrointestinal tract or following other modes of administration, and is stored in all tissues, especially the liver, brain, kidney, and heart. Under normal conditions there is probably little destruction of thiamine in the digestive tract, although intestinal disturbances may seriously retard absorption of this vitamin. The possibility of thiamine being synthesized by the bacterial flora of the gastrointestinal tract must not be overlooked. It should also be mentioned that the ingestion of live yeasts may render thiamine consumed in other foods unavailable for human beings (Parsons et al., 1945).

The capacity to store thiamine is rather small, and thus its absence in the diet causes the limited reserve to become depleted quickly. Symptoms of deficiency, however, do not appear for several weeks or even months after depletion has occurred. High vitamin B_1 diets increase the store for several weeks, excess being eliminated in the urine. Thiamine is also *destroyed* in the body, the rate being increased by increasing the metabolic rate, whether by exercise, administration of thyroid, or by other means.

TABLE XXVIII

THE VITAMINS

VITAMINS	OCCURRENCE	POSSIBLE EFFECTS OF DEFICIENCY	DAILY REQUIREMENTS	THERAPEUTIC DOSAGE
Vitamin A	Cod liver oil, halibut liver oil, and other fish liver oils, green leafy vegetables, yellow vegetables, liver, eggs, milk, butter, apricots, yellow peaches, oranges, and bananas	Nyctalopia (night blindness) Xerophthalmia Dermatosis Nervous system changes Keratomalacia	Not yet satisfactorily determined. Possibly 3,000 to 5,000 International Units Protective: children, lactating women, etc., 6,000 to 8,000 I.U. daily	Recommended prophylactic dose: equivalent of at least 2 teaspoonfuls of cod liver oil but not more than 10,000 U.S.P. units daily. Larger doses, not exceeding 50,000-100,000 I.U., may be necessary in treatment of deficiency states.
Vitamin B_1 (Thiamine Hydrochloride, U.S.P.)	Yeast, whole grains (germ and outer layers of seeds), pork, liver, organs and muscles of many animals, nuts, eggs, legumes, and most vegetables	Beriberi Gastrointestinal phenomena Polyneuritis of alcoholism, pregnancy and pellagra Certain cardiovascular phenomena Arrested growth in infants and children	Adults: 1 to 2.5 mg. Children: 0.03 mg. for each 100 calories Infants: 0.15 to 0.5 mg.	10 to 50 mg. daily in acute deficiencies.
Riboflavin (U.S.P.) (Vitamin B_2)	Yeast, milk, liver, wheat germ, eggs, cheese, green leafy vegetables, peas, lima beans, organs and muscles of many animals	Cheilosis Glossitis Seborrheic lesions about eyes and nose Loss of weight Photophobia	Adults: 3 mg. Children: 1 mg.	Suggested: 3 to 15 mg. daily, depending on severity of the deficiency.

Nicotinic Acid (U.S.P.) (and Amide, U.S.P.)	Yeast, liver, wheat germ, milk, organs and muscles of many animals, fish, egg yolk, kale, peas, tomatoes, turnips	Pellagra Characteristic dermatitis Glossitis Gastrointestinal disturbances Central nervous system disturbances	Not yet satisfactorily determined 15-20 mg. recommended for adults	Varies considerably. An effective dosage is 500 mg. daily in 10 doses of 50 mg. each.
Vitamin C (Ascorbic Acid, U.S.P.)	Oranges, lemons, limes, tomatoes, grapefruit, raw cabbage, peppers, turnips	Scurvy Defective teeth Prescorbutic conditions	Adults: 50 to 75 mg. Infants: 10 to 50 mg.	Adults: 50 to 200 mg. daily. Infants: 30 to 60 mg. daily. (Larger doses, up to 500 mg. daily, have been recommended.)
Vitamin D	Cod liver oil and some other fish liver oils, eggs, butter and milk	Infantile rickets Spasmophilia (infantile tetany) Osteomalacia Osteoporosis (associated condition) Abnormal dentition Abnormal calcium and phosphorus metabolism	Not yet satisfactorily determined. Approx. 800-1200 international units	1200-5000 international units. (Larger doses, up to 60,000 units, may be required.)
		NEWER VITAMINS		
Vitamin B_6 (Pyridoxine)	Yeast, liver, tikitiki, rice bran, wheat germ, kidney, and muscle	Significance in human nutrition not yet established Dermatitis in rats Anemia in dogs	Undetermined (probably 1.5 mg.)	Undetermined.

TABLE XXVIII—CONT'D

VITAMINS	OCCURRENCE	POSSIBLE EFFECTS OF DEFICIENCY	DAILY REQUIREMENTS	THERAPEUTIC DOSAGE
Pantothenic Acid	Yeast, liver and other tissues, wheat germ, rice bran, egg yolk, and wheat bran	Significance in human nutrition not yet established Dermatitis in chicks Hemorrhagic adrenals and achromotrichia in rats	Undetermined Probably about 10 mg.	Undetermined. Suggested dose 10 to 50 mg. of calcium pantothenate
Vitamin K_1 (2-Methyl-3-Phytyl-1, 4-Naphthoquinone)	Alfalfa, kale, spinach, dried carrot tops, tomatoes, fish meal, hog liver, soy bean oil, and some other vegetable oils	Prothrombin deficiency Prolonged clotting time Hemorrhagic diathesis in newborn, and in hepatic and biliary disease	Undetermined	1 to 2 mg.
Menadione 2-methyl-1, 4-naphthoquinone (U.S.P.) (Vitamin K activity)	A pure chemical compound which exhibits marked vitamin K activity. Has not been isolated from foodstuffs	See Vitamin K_1	Undetermined	1 to 2 mg.
Alpha-Tocopherol (Vitamin E)	Wheat germ oil, cottonseed oil, and green leafy vegetables	Significance in human nutrition not yet established Investigative studies suggest limited value in certain cases of progressive muscular dystrophy and amyotrophic lateral sclerosis Necessary to ensure normal course of pregnancy and to prevent paralysis in the rat Necessary for normal growth of young rats	Uncertain Doses of 4 to 15 cc. of wheat germ oil daily or 3 to 12 mg. of alpha-tocopherol daily frequently employed	50 to 100 mg. daily.

Function of Thiamine.—Thiamine occurs in food and tissues in the free form and as thiamine pyrophosphate or cocarboxylase. In the latter form it functions in the living cell as a coenzyme in carbohydrate metabolism. In thiamine deficiency the utilization of carbohydrates is incomplete and pyruvic acid accumulates in the tissues, a condition which is used to determine thiamine deficiency. It is essential for the maintenance of normal nerves, appetite and digestion, circulation, and normal growth.

Clinical Manifestations of Vitamin B_1 Deficiency.—Vitamin B_1 deficiency affects predominantly the peripheral nervous system, the gastrointestinal tract, and the cardiovascular system. The symptoms usually are as follows:

Mild	*Moderate*	*Severe*
Anorexia	Loss knee jerk	Central neuritis
Fatigue	Calf muscle atrophy	Edema
Leg cramps	Foot drop	Enlarged heart
Burning feet		
Plantar hyperesthenia		
Loss ankle jerk		

Vitamin B_1 deficiency in an adult is usually characterized by an insidious onset and many of the mild symptoms listed above. Manifestations of neuritis may appear associated with muscle weakness and tenderness, especially of the calf muscles. The above symptoms usually respond rapidly to treatment, and the pain frequently disappears in from two to three days. Sensation and reflexes return to normal in a somewhat longer period.

Symptoms of beriberi may less frequently occur. Spies, Vilter, and Ashe believe a diagnosis of beriberi requires that the patient have evidence of peripheral neuritis, with or without edema, cardiovascular and gastrointestinal abnormalities, and a history of a diet deficient in B_1.

Beriberi is usually acute in the infant. There is often a history of a sudden onset with body rigidity. Loss of appetite, constipation, vomiting, general weakness, enlarged heart, edema, cyanosis, and a rapid irregular pulse are common symptoms. Administration of vitamin B_1 produces a rapid and dramatic response.

Therapeutic Uses.—Thiamine is indicated for the prevention and treatment of **beriberi**, and for the prevention and treatment of *anorexia* due to vitamin B_1 deficiency.

Thiamine is probably of value in the treatment of alcoholic neuritis, the neuritis of pellagra, and the neuritis of pregnancy, although its deficiency is not the sole cause of these conditions.

Thiamine is also indicated in certain conditions, e.g., vomiting of pregnancy, severe diarrhea, etc., which prevent proper assimilation of this vitamin.

Treatment of Acute Deficiences.—Deficiencies respond rapidly to liberal amounts of thiamine. The diet should include large amounts of whole cereals and vegetables, and supplementary thiamine hydrochloride should be given until the symptoms have disappeared. Parenteral administration is indicated when absorption from the gut is impaired. In severe cardiac failure, severe peripheral neuritis, or severe gastrointestinal disturbances, the parenteral route is usually the method of choice. Thiamine hydrochloride may be administered subcutaneously or intravenously, 10 to 50 mg. daily for a few days. Then 10 mg. given by injection twice a week may suffice, or 5 mg. by mouth daily.

Diagnosis of Deficiency.—Diet history, clinical symptoms and signs, determination of urinary excretion, and therapeutic trial determine the diagnosis.

Vitamin B_1 Requirements.—

Protective:	1 to 3 mg.
Curative:	10 to 50 mg. daily

Common Units: One milligram of thiamine (B_1) = approximately 333 international units (I.U.). The U.S.P. official method of assay of vitamin B_1 preparations involves the use of rats rendered polyneuritic by a test diet.

Sources of Vitamin B_1.—*Dietary:*

Brewer's yeast	10.0 mg. per 100 Gm.
Molasses	2.0 mg. per 100 Gm.
Kidney beans	1.0 mg. per 100 Gm.
Peanuts	0.5 mg. per 100 Gm.
Liver	0.5 mg. per 100 Gm.
Lean pork	0.3 mg. per 100 Gm.

SPECIAL SOURCES

Thiamine Hydrochloride, *Thiaminae Hydrochloridum*, U.S.P. *Dosage:* 5 mg. ($\frac{1}{12}$ grain) (U.S.P.).

Thiamine Hydrochloride Injection, *Injectio Thiaminae Hydrochloridi*, U.S.P. *Dosage:* 10 mg. ($\frac{1}{6}$ grain) thiamine hydrochloride (U.S.P.)

Thiamine Hydrochloride Tablets, *Tabellae Thiaminae Hydrochloridi*, U.S.P. *Dosage:* The usual sizes contain 3 mg., 5 mg., and 10 mg.

Hexavitamin Capsules, *Capsulae Hexavitaminarum*, U.S.P.—Each capsule contains not less than 5,000 U.S.P. units of vitamin A from natural (animal) sources, 400 U.S.P. units of vitamin D from natural (animal) sources or as activated ergosterol or activated 7-dehydrocholesterol, 75 mg. ascorbic acid, 2 mg. thiamine hydrochloride, 3 mg. riboflavin, and 20 mg. nicotinamide. *Dosage:* To be determined by the physician in accordance with the needs of the patient (U.S.P.). Each capsule supplies an approximately adequate daily allowance of the six vitamins for adult men.

Hexavitamin Tablets, *Tabellae Hexavitaminarum*, U.S.P. Same strength as above capsules.

Triasyn B Capsules, *Capsulae Triasyni B*, U.S.P.—Each capsule contains thiamine hydrochloride 2 mg., riboflavin 3 mg., and nicotinamide 20 mg. *Dosage:* Each capsule supplies an approximately adequate daily allowance of the three vitamins for adult men.

Triasyn B. Tablets, *Tabellae Triasyni B*, U.S.P.—Same strength as above capsules.

Wheat Germ is a rich source of Vitamin B_1 and other B factors.

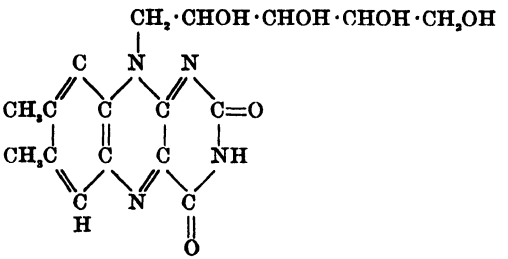
Yeast contains vitamin B_1 and other vitamin B factors.

The N.N.R. contains ampuls, tablets, and solutions of thiamine hydrochloride.

Riboflavin

Riboflavin, formerly known as lactoflavin, vitamin B_2, and vitamin G, has the empirical formula: $C_{17}H_{20}N_4O_6$. The chemical nature of this substance was established in 1935. The following year the Council ac-

cepted it for standardization and experimental purposes. Since that time sufficient evidence has been accumulated to justify its acceptance in the U.S.P. Its structural formula is as follows:



Riboflavin belongs to a group of yellow fluorescent pigments called flavins and is one of the heat-stable factors of the vitamin B complex. This factor is responsible for a part of the growth-promoting property of the B_2 complex, but it has no antidermatitis action. It appears as orange-yellow needles and is very soluble in water. It is not soluble in oil solvents, and is readily decomposed by light.

Riboflavin is distributed throughout all the body tissues, the amount in the various organs remains remarkably constant irrespective of intake in the dietary. When in normal health, man excretes the vitamin in measurable quantity in the urine. In lactating animals, a relatively large amount of riboflavin (20 per cent of dietary intake) appears in the milk. There is considerable evidence for the synthesis of riboflavin in the intestinal tract and that some of this riboflavin can be utilized.

Prevalence of Deficiency.—According to clinicians, riboflavin deficiency is one of the most prevalent avitaminoses. Riboflavin deficiency is likely to be associated with other vitamin deficiencies, especially with those of thiamine and niacin since these water-soluble vitamins often occur together in natural foodstuffs.

Function of Riboflavin.—A deficiency of riboflavin results in retardation of growth; but it must be remembered that it is no more important in contributing to growth than many other essential substances. Riboflavin also exerts important effects on the nervous system, the precise effects have not as yet been elucidated. This vitamin is important in the nutrition of the skin, being necessary in the normal sensory acuity of the skin. Various lesions of the eye, such as cataract, corneal opacity, and ulcer, have been attributed to lack of riboflavin.

Mode of Action.—Riboflavin acts as an enzyme in the oxidation processes of living cells, probably acting together with thiamine in the oxidation of pyruvic acid.

Clinical Manifestations of Deficiency.—The prodromal symptoms of riboflavin deficiency have not been completely differentiated from those of beriberi, pellagra, and other deficiency diseases with which they are frequently associated. There are two types of lesions which so far have been identified quite satisfactorily with riboflavin deficiency.

1. *Skin Lesions.*—A typical glossitis may be the initial sign of riboflavin deficiency. In contrast to the glossitis of pellagra, the tongue is clean, the papillae are flattened or mushroom-shaped rather than atrophic, and the color is definitely magenta. Later, the lips become

reddened, then shiny and denuded, with maceration and fissuring at the angles of the mouth (cheilosis). Granulation tissue heaps up in the ulcerated areas and the edges are surrounded by yellowish crusts. Similar lesions may be found in the nasolabial folds, extending up into the nostrils. The above symptoms respond promptly to riboflavin therapy.

2. *Ocular Manifestations.*—Persons with riboflavin deficiency may have excessive lacrimation, photophobia, burning and blurring of vision. Other eye symptoms include congestion of the sclera, vascularization, opacities of the cornea, abnormal pigmentation of the iris, and interstitial keratitis. These symptoms, when due to riboflavin deficiency, are promptly relieved by riboflavin therapy.

3. *Nonspecific Manifestations.*—Digestive disturbances, nervous depression, increased susceptibility to infection, diminished vitality, and early senescence.

Therapeutic Uses.—The therapeutic dosage of riboflavin necessarily varies with the degree of deficiency. Most deficiencies respond favorably to the oral administration of 2 to 10 mg. daily in divided doses. In the presence of gastric achlorhydria, diarrhea, or severe hepatic disease, 10 to 15 mg. daily may be indicated. No untoward symptoms have been observed following the use of relatively larger doses.

Riboflavin is recognized as a specific in the treatment of certain characteristic lesions of the tongue, lips, and the face, which result from a deficiency of this vitamin. This deficiency responds to riboflavin given orally or intravenously in doses of 1 to 2 mg. three times a day. Treatment must be continued for many weeks since healing of the lesions is slow and relapses are frequent.

The ocular manifestations of riboflavin deficiency are treated as indicated for the skin conditions.

Riboflavin is also recommended in the treatment of pellagra. It is also indicated in conditions of retarded growth as being one of many important substances necessary for normal growth. During pregnancy and lactation 5 mg. of riboflavin may be administered orally once daily.

Recent studies in the Nutrition Clinic at the Hillman Hospital in Birmingham indicate that riboflavin is the most common deficiency which occurs in malnourished infants and children in that area. Riboflavin deficiency should be expected in all chronically malnourished persons.

Diagnosis of Deficiency.—Diagnosis may be assisted by studying the diet of the patient. Symptoms and signs are also of great value. Slit lamp examination of the cornea is clinically of value. Apply therapeutic test.

Riboflavin Requirements.—Probable normal requirements are: children 1 mg. daily, adults 3 mg. daily.

Common Unit: A U.S.P. Riboflavin Reference Standard is available. Preparations are standardized by a microbiologic assay employing *Lactobacillus casei* as the best organism. One milligram of riboflavin equals 400 Sherman units of vitamin G (B_2).

Sources of Riboflavin.—

Liver	1.0 mg. per 100 Gm.
Yeast	1.0 mg. per 100 Gm.
Wheat germ	0.2 mg. per 100 Gm.
Egg	0.2 mg. per 100 Gm.
Green vegetables	0.1 mg. per 100 Gm.
Beef	0.1 mg. per 100 Gm.

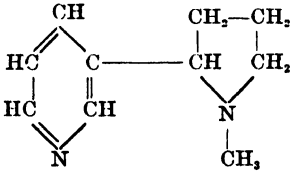
SPECIAL SOURCES

Riboflavin, *Riboflavinum*, U.S.P. *Dosage:* 5 mg.
Riboflavin Injection, *Injectio Riboflavini*, U.S.P. *Dosage:* 5 mg. riboflavin (U.S.P.) usually available in ampuls containing 0.2 mg. in 1 cc., 1 mg. in 2 cc., and 5 mg. in 1 cc.
Riboflavin Tablets, *Tabellae Riboflavini*, U.S.P. The usual sizes contain 1 mg. and 5 mg.
Riboflavin, N.N.R.
Hexavitamin Capsules, *Capsulae Hexavitaminarum*, U.S.P.
Hexavitamin Tablets, *Tabellae Hexavitaminarum*, U.S.P.
Triasyn B Capsules, *Capsulae Triasyni B*, U.S.P.
Triasyn B Tablets, *Tabellae Triasyni B*, U.S.P.

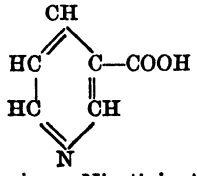
Niacin or Niacinamide

(Nicotinic Acid or Nicotinic Acid Amide)

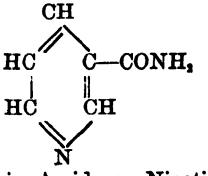
Nicotinic acid, pyridine 3-carboxylic acid, $C_6H_5O_2N$, occurs as white needle-like crystals which are odorless and possess a slightly bitter taste. It is soluble in water (1:60). Nicotinic acid is one of the most thermostable members of the B complex, and it may be sterilized by heat. Since nicotinic acid is a very stable compound, there is little destruction during cooking and the loss is negligible unless the cooking water is discarded. It is not as inert in the body as are other vitamins, due to the rather marked pharmacological activity inherent in pyridine derivatives as a whole. Nicotinic acid, although related chemically to nicotine, does not exhibit the action upon the autonomic nervous system characteristic of the latter substance and is relatively nontoxic. Nicotinic acid, its amide, and its sodium salt are equally effective in the treatment of pellagra. The structural formulas of nicotine, nicotinic acid, and the amide are as follows:



Nicotine



Niacin or Nicotinic Acid



Niacin Amide or Nicotinic Acid Amide

Nicotinic acid is readily absorbed from the gastrointestinal tract and following parenteral administration. Vilter, Spies and Mathews (1938) found nicotinic acid or related compounds to be absent from the urine of pellagrins but present in the urine of normal subjects.

Function and Mode of Action.—Nicotinic acid in the form of the amide is essential in human nutrition as a constituent of a coenzyme

system necessary for normal cell metabolism. Nicotinic acid is apparently involved in sulfur metabolism, being essential in the synthesis of glutathione. Although the exact mechanism of its action is unknown, it undoubtedly bears a relation to the health of epithelial and nervous tissue.

Clinical Manifestations of Deficiency.—Evidence is convincing that nicotinic acid deficiency leads to the clinical condition known as pellagra. It is not certain whether pellagra represents a single or multiple deficiency, but the onset of the important symptoms can be prevented by adding nicotinic acid to a pellagra-producing diet.

Pellagra is a deficiency disease which affects primarily the skin, alimentary tract, and the nervous system. In the early stages of the disease pellagrins complain of headaches, nervousness, irritability, constipation, itching and burning of the skin, burning of the tongue, and repeated gastrointestinal upsets.

The skin lesions are characterized by an erythematous cutaneous eruption resembling sunburn which first appears on the back of the hands, then eventually involves the forehead, neck, and feet. The cutaneous lesions, which are characteristically symmetrical, may remain dry and eventually become scaly or pigmented, or bullae may form at the center and become infected, resulting in indolent ulcers.

Stomatitis, enteritis, and diarrhea are characteristic gastrointestinal symptoms. Nausea and vomiting are also common. The symptoms referable to the nervous system consist of dizziness, insomnia, headache, depression and loss of memory. Peripheral motor and sensory nerve disturbances are common.

Toxicology: Unfavorable symptoms may follow the administration of nicotinic acid. The most common are sensations of tingling and burning in the extremities, flushing of the face, and various skin eruptions. Excitement and palpitation may occur. A dose of 100 mg. may give rise to the above-mentioned symptoms. The amide (nicotinamide) has become the preferred form because it can be given in large amounts without the tendency to produce peripheral vasodilatation.

Therapeutic Uses.—Nicotinic acid (or amide) is recognized as a specific only in the treatment of pellagra. Pellagra should be suspected in malnourished patients presenting the classic symptoms. Whenever there is doubt regarding diagnosis, 100 mg. of nicotinic acid, given orally five times a day for several days, will serve as a therapeutic test.

Nicotinic acid (or amide) is indicated in the prophylaxis and the treatment of pellagra. In *acute exacerbations* of the disease Spies and co-workers (1938) recommend 50 mg. given ten times daily. If oral administration is contraindicated, intravenous injection of 20 mg. in 2 cc. of physiological sodium chloride is given two or three times daily. For *prophylactic treatment* the dose can be determined only by trial. Spies and co-workers found that the required dose varied from 50 mg. daily to as high as 1,000 mg. daily. In the treatment and in prophylaxis it is recommended that thiamine chloride and riboflavin be administered with the nicotinic acid (or amide). A good diet containing natural sources of the vitamins of the B complex is also indicated. *Side reactions* following nicotinic acid therapy are usually few and comparatively mild. Reactions may usually be minimized by more frequent dosage or by the employment of the amide.

Dosage: Experience has demonstrated that the daily oral administration of 500 mg. of niacin or niacinamide in 10 doses of 50 mg. each is safe and effective in pellagra. The parenteral dose may vary from 40 to 80 mg., dissolved in sterile physiological saline and given by vein

in divided doses. If pure compounds are not available, powdered brewer's yeast, 30 to 200 Gm. daily, may be substituted.

Diagnosis of Deficiency.—Diet history and early symptoms and signs are useful in diagnosis of nicotinic acid deficiency. The therapeutic trial is very useful and easy to apply. No satisfactory laboratory tests are yet available.

Nicotinic Acid (or Amide) Requirements.—

Prophylactic:	20 mg. daily
Protective:	50 mg. daily
Curative:	150-500 mg. daily

Common Unit: The milligram unit.

Sources of Nicotinic Acid.—*Dietary:* Rich sources are yeast, liver, and milk. Good sources are wheat germ, meat, fish, egg yolk, kale, peas, tomatoes, turnips, and peanuts. Corn, soy beans, and molasses are practically devoid of this vitamin.

SPECIAL SOURCES

Nicotinic Acid, *Acidum Nicotinicum* (Niacin), U.S.P. *Dosage:* 25 mg. (⅜ grain). New and Nonofficial Remedies gives dosage for therapeutic purposes as 0.5 Gm. (8 grains) in ten doses of 50 mg. (⅝ grain) each.

Nicotinic Acid Tablets, *Tabellae Acidi Nicotinici,* U.S.P. (Niacin Tablets). The usual sizes contain 25 mg., 50 mg. and 100 mg.

Nicotinamide, *Nicotinamidum,* U.S.P. *Dosage:* 25 mg. (⅜ grain).

Nicotinamide Injection, *Injectio Nicotinamidi,* U.S.P. *Dosage:* Parenteral, 100 mg. nicotinamide. Usually available in ampuls containing either 50 or 100 mg. per cubic centimeter. The official dose provides about five times the recommended daily allowance for adult men.

Nicotinamide Tablets, *Tabellae Nicotinamide,* U.S.P. Usual sizes contain 25 mg. and 50 mg.

Rice Polishings, *Perpolitiones Oryzae,* U.S.P. (Rice Bran, Tikitiki).

Rice Polishing Extract, *Extractum Perpolitionum Oryzae,* U.S.P. *Dosage:* 8 cc. (2 fluidrachms).

Hexavitamin Capsules, *Capsulae Hexavitaminarum,* U.S.P.

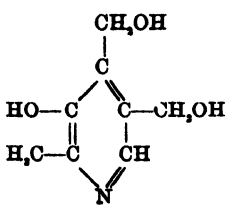
Hexavitamin Tablets, *Tabellae Hexavitaminarum,* U.S.P.

Triasyn B Capsules, *Capsulae Triasyni,* U.S.P.

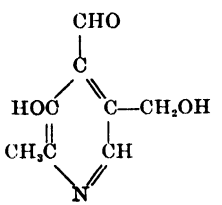
Triasyn B Tablets, *Tabellae Triasyni,* U.S.P.

Pyridoxine (Vitamin B_6)

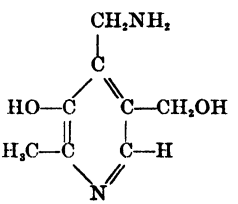
Pyridoxine ($C_8H_{11}NO_3$), another component of the vitamin B complex, is known to be essential in animal nutrition. It occurs in relatively large amounts in yeast, liver, tikitiki, rice bran, and wheat germ. Kidney



Pyridoxine (Vitamin B_6)



Pyridoxal



Pyridoxamine

and muscle are very rich sources. It has been available in crystalline form for experimental use since the spring of 1939. Its structural formula indicates the relation to nicotinic acid (pyridine derivative).

In 1944 it was shown by Snell and associates that two derivatives of pyridoxine, namely, pyridoxal and pyridoxamine, were more active than the original compound. All three compounds occur in natural materials, although many tissues, particularly animal tissues, and yeast contain predominately pyridoxal and pyridoxamine.

Birch (1938) presented evidence to show that pyridoxine may function in some way in the utilization of unsaturated fatty acids. In addition to skin lesions, which characterize the deficiency in rats, a lack of pyridoxine in dogs and swine produces a microcytic hypochromic anemia which responds to pyridoxine therapy. Pyridoxine is probably also important in fundamental oxidation processes.

No clear-cut symptoms resulting from pyridoxine deficiency have been described in human beings. Nervousness, insomnia, and ataxia are usually present. Spies (1939) reported an additional improvement in pellagrins with pyridoxine therapy after treatment with nicotinic acid, thiamine, and riboflavin. Smith and Martin (1940) observed a rapid healing of typical lesions of cheilitis with vitamin B_6 therapy.

The administration of pyridoxine is reported to be useful in idiopathic parkinsonism and muscular dystrophies. It has also been claimed to be useful in the alleviation of vomiting in pregnancy and in roentgen sickness.

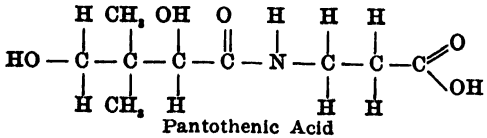
The optimum dose of vitamin B_6 in the treatment of various conditions has not been established. The single doses described in current reports have ranged from 10 to 100 mg. given either orally or parenterally. Acute or chronic toxicity studies on animals have shown pyridoxine to be a substance of low toxicity, similar in this respect to the other members of the B complex.

Pyridoxine Requirements: Human requirement is unknown, but animal experiments indicate that vitamin B_6 requirement may be about the same as thiamine—about 1.5 mg. a day.

The most reliable method of determining the B_6 content of foods is probably the rat assay method (Conger and Elvehjem, 1941).

Pantothenic Acid (Filtrate Factor)

Pantothenic acid ($C_9H_{17}NO_5$), one of the members of vitamin B complex isolated from the so-called "filtrate factors," has not as yet been associated with a specific syndrome in human beings. It is found in relatively large amounts in yeast, liver, wheat germ, rice bran, egg yolk, and wheat bran. Pantothenic acid was isolated in 1938 and synthesized in 1940. Its structural formula is



Pantothenic Acid

Pantothenic acid is fairly stable when subjected to moist heat, especially at a neutral pH, but is destroyed by prolonged dry heat. It is widely distributed in nature, and recent work has shown that much of the vitamin may be present in bound forms.

Lipman and his co-workers (1947) have shown that pantothenic acid is related to enzymatic acetylation. If pantothenic acid is related to all biologic acetylations, it has a very important function.

The various observations indicate that pantothenic acid is essential to human nutrition and that its function is probably associated with that of riboflavin. As much as 100 mg. of calcium or sodium pantothenate has been administered intravenously in human beings without producing any significant changes in blood pressure or respiration. Pantothenic acid deficiency in chicks produces a characteristic type of dermatitis. Deficiency of this factor has also been associated with adrenal hemorrhage, atrophy and necrosis in rats, and also with a nutritional achromatrichia in rats.

No specific symptoms in human beings have been correlated with a deficiency of this vitamin. This may be due to the fact that pantothenic acid is widely distributed and that even restricted diets may not be low enough to cause a serious deficiency. The daily requirement is probably about 10 mg. The suggested dose is 10 to 50 mg. orally of calcium pantothenate.

Choline

Choline is a colorless viscous fluid, and the more familiar choline chloride is a hygroscopic white crystalline substance. Choline is now considered an important member of the B complex. It functions in some way to aid in the mobilization of fatty acids in the body since in its absence liver fat rapidly accumulates. McHenry (1941) states that there is evidence now that choline may function in at least three ways: (1) to stimulate the formation of phospholipids, (2) to make possible the production of acetylcholine, and (3) to supply labile methyl groups.

By far the best dietary source of choline is egg yolk, while soy bean meal, liver, dried yeast, pancreas, brain, and kidney are good sources. Most edible fats are low in choline. Most diets contain sufficient choline to meet ordinary needs. However, there is evidence that some types of clinical cirrhosis are favorably affected by dietary treatment including choline and other vitamins, together with a high protein diet.

The *choline requirement* is difficult to establish. From animal experiments one might suggest that the human requirement would be less than 500 mg. per day. It has been estimated that the choline intake from an average diet may range from 250 to 600 mg. (Elvehjem, 1948).

Biotin (Vitamin H)

Although biotin has been recognized as necessary for the growth of bacteria for some time, its significance in animal nutrition is just in the process of being elucidated. Biotin was first isolated by Kögel and Tonnis (1936), and its empirical formula $C_{10}H_{16}O_3N_2S$ has been found by Vigneaud (1942) to consist of a cyclic derivative of urea.

Biotin is widely distributed in foods of both plant and animal origin, including seeds and nuts. Richest sources are liver, kidney, and eggs. Milk contains an appreciable amount. It is a very stable compound, resisting autoclaving with strong mineral acids. The pure biotin, however, shows appreciable lability to alkali.

Of interest is the "egg white injury" which has been demonstrated in animals and is due to the unavailability of biotin in the presence of egg albumin by virtue of being tied up with avidin, in which complex biotin cannot be absorbed from the intestine and is excreted in the feces.

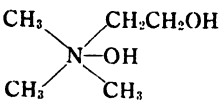
Recent work has established a fairly definite role for biotin in metabolism. It apparently functions in carboxylation of pyruvate to yield oxalacetate. Shive and his co-workers (1947) and Lardy and his associates (1947) have shown that either oxalacetate or aspartate can partially replace biotin in the nutrition of Lactobacillus arabinosus.

While rather definite requirements can be established for chickens, it is difficult to establish the requirements for man since a large part may be supplied by the intestinal flora. Sydenstricker and his co-workers (1942) reported that dermatitis and changes in the color of skin which responded to biotin were produced in human subjects by feeding diets with high levels of egg white.

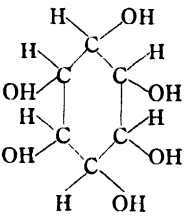
Much fundamental work must be done before the clinical significance of biotin can be established. At least, it is evident now that there probably is sufficient biotin present in the average diet of human beings.

Inositol

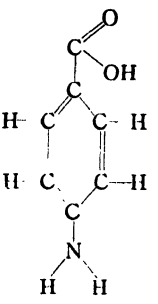
Inositol ($C_6H_{12}O_6$) is a crystalline substance, the formula of which is isomeric with d-glucose. Its structure shows it to be a hexahydroxy-cyclohexane.



Choline



Inositol



p-Aminobenzoic Acid

Inositol is an extremely stable compound. It is found in all living tissues. Good sources are cereal grains, green leaves, and citrus fruits. Lack of it in small animals results in severe loss of hair followed by dermatitis. Little is known regarding the role of inositol in human nutrition. Perhaps the most interesting development is the report of Milhorat and Bartels (1945) that inositol may improve the action of tocopherol in the treatment of muscular dystrophy.

Para-Aminobenzoic Acid

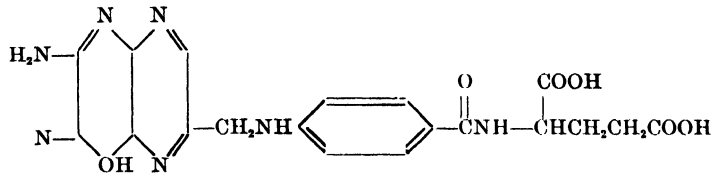
Another factor first identified with its effect on bacterial growth and which now shows indication of a vitamin-like action in animals is para-amino-benzoic acid. Ansbacher (1941) has produced graying of the fur of rats on a ration which could be cured by the administration of this vitamin. A growth response in chicks has also been obtained by the addition of para-aminobenzoic acid to the diet. The relation of para-aminobenzoic acid to the mode of action of the sulfonamide drugs is discussed in the chapter on the Sulfonamide Drugs.

Interesting observations on the chemotherapeutic effects of para-aminobenzoic acid on the effect of typhoid (Yeomans et al., 1944) and against Rocky Mountain spotted fever (Flinn et al., 1946) have been reported.

VITAMINS VS. HAIR COLOR.—There seems to be some support for the belief that there is some relationship between the intake of vitamins and the graying of hair. Just what that relationship is we do not know. However, of all the factors that have been reported thus far (calcium pantothenate, para-aminobenzoic acid, biotin, inositol) calcium pantothenate seems to offer more promise than any of the others. The possible role of para-aminobenzoic acid in the treatment of gray hair in human beings has been studied by Brandaleone and his associates (1943). They reported that in a group of nineteen elderly persons with gray hair only two showed significant color change during a period of intensive vitamin study. We shall all watch with a good deal of interest the subsequent reports on this subject.

Folic Acid

Chemically, folic acid is pteroyl glutamic acid, a yellow compound sparingly soluble in water with the following structural formula:



Three groups are present in the above molecule: the pteridine part, para-aminobenzoic acid, and glutamic acid.

Folic acid is widely distributed in nature both in free form and in compounds with added glutamic acid such as pteroyl triglutamic acid and pteroyl heptaglutamate.

At present it is established that synthetic glutamic acid is required for growth and blood formation in chicks, monkeys, and fox and mink. Rats do not require folic acid in the diet until the synthesis of this compound by intestinal bacteria is reduced through the use of sulfonamide drugs. The human being apparently is satisfied by intestinal production except under disturbed conditions.

In human beings the beneficial affect of synthetic folic acid in various types of macrocytic anemia in relapse has been demonstrated. Darby (1947) has described the beneficial effects of pteroyl glutamic acid on the gastrointestinal manifestations of sprue and related syndromes.

The folic acid requirements of human beings is difficult to estimate. Clinical responses have been obtained with 2 to 10 mg. On the basis of animal requirements, a figure of 0.1 to 0.2 mg. per day may be suggested (Elvehjem, 1948).

Additional Factors

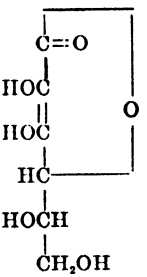
The existence of several additional factors in the vitamin B complex is evident from various animal studies. Although space will not permit discussion of these important substances, brief mention will be made of *vitamin* B_{11}. This substance has been isolated from liver as a crystalline compound. It is highly active in patients with Addisonian pernicious anemia (West, 1948). This compound is also active for the growth of *Lactobacillus lactis* (Short, 1948).

Ascorbic Acid (Vitamin C)

Scurvy, a deficiency disease known since the time men first began to sail ships, was first accurately described in literature by James Lind,

a practitioner of Edinburgh, in 1753. It was largely through the influence of this man that scurvy was eliminated from the British Navy by supplying the sailors with a daily ration of lemon and lime juice. To Holst and Fröhlich (1907) belongs the credit for producing scurvy experimentally in guinea pigs upon which is based the bio-assay of the antiscorbutic vitamin. To the combined efforts of many investigators we owe our knowledge of many of the properties of this vitamin.

Ascorbic acid was isolated by Szent-Györgyi in 1928 from oranges, lemons and from the suprarenal cortex. About the same time King and Waugh isolated crystals of ascorbic acid from concentrates of lemon juice. It was later synthesized by Hirst and associates who gave it the following formula:



Ascorbic Acid ($C_6H_8O_6$)
(Vitamin C)

Ascorbic acid is soluble in water and alcohol and is readily destroyed by heat and oxidative processes. Prolonged boiling, drying, aging, or storage reduces its antiscorbutic properties.

Ascorbic acid is readily absorbed from the normal intestinal tract. It is distributed to all body tissues, the highest concentrations being found in muscle and stored fat. After absorption, the ascorbic acid content of the blood rises. A blood level of vitamin C of from 1.0 to 2.0 mg. per cent is completely saturated, levels of 0.5 mg. are considered a low normal, and blood values below 0.15 mg. are invariably associated with clinical scurvy. Ascorbic acid is partially destroyed and partially excreted in the urine and sweat. There is a renal threshold for vitamin C which is approximately 1.4 mg. per cent. When the body is saturated the blood and urine contain about the same concentration of vitamin. If more vitamin C is administered, most of it escapes into the urine.

Function and Mode of Action.—Ascorbic acid produces the following effects: (1) it functions in intracellular oxidation-reduction processes, i.e., serving as a hydrogen transport agent (King, 1936); (2) it aids in the formation of colloidal supporting structure (collagen) of the bones, muscle, teeth, blood vessels, red blood corpuscles, etc.; (3) it improves appetite and stimulates growth; (4) it is essential to normal tissue metabolism and tissue respiration; (5) it apparently exhibits a specific and essential effect on glandular functions and acts protectively on the vascular system, and (6) it is apparently involved in the defensive mechanisms of the body against bacterial toxins and perhaps other poisons.

Farmer, Abt, and associates (1941) found ascorbic acid a preventive of cutaneous reactions caused by neoarsphenamine. They postulate that if the ascorbic acid in the circulatory blood is maintained at a sufficiently high level in hypersensitive patients, toxic cutaneous reactions may be inhibited.

Clinical and experimental evidence suggests that vitamin C plays an important role in wound healing and tissue repair. Lack of vitamin C prevents fibroblasts from forming collagenous connective tissue, causes weakness in the capillaries and bones, tends to cease growing due to the inability of osteoblasts to form normal tissue.

Occurrence of Vitamin C Deficiency.—Severe vitamin C deficiency, fortunately, is uncommon in the United States. The general use of antiscorbutic foods has been largely responsible for the prevention of advanced stages of this disease.

On the other hand, subclinical avitaminosis C is fairly prevalent today. Loss of vitamin C by cooking, restricted diets, and abnormalities of absorption, all contribute to this deficiency.

Clinical Manifestations of Vitamin C Deficiency.—

1. *Scurvy.*—Scurvy is characterized by degenerative changes in the connective tissues, increased capillary permeability, and hemorrhages in various tissues, i.e., mucous membranes of the mouth, gastrointestinal tract, skin, subcutaneous tissues, muscles, subperiosteal tissues and other parts of the body. A characteristic clinical sign is the position assumed by the infant in bed, i.e., flexion, wide abduction, and external rotation of legs; extreme pain caused by subperiosteal hemorrhages may account for this position. The gums are swollen and red and may almost cover the teeth. Bleeding gums and extravasation into the mucous membranes are common. In adults petechial hemorrhages into the skin are frequently observed. Brownish tender swellings may appear due to bleeding into the muscles.

Subclinical scurvy: This condition may be difficult to diagnose. Probably the most frequent clinical sign of vitamin C deficiency is gingivitis. Other nonspecific signs are vague pains in the extremities, slight pallor or anemia, weakness, malaria, anorexia and lack of growth and loss of weight.

2. *Anemia.*—It has been reported that deficiency of vitamin C often leads to anemia of a normocytic or slightly macrocytic type, which, when uncomplicated, responds to vitamin C therapy, but not to liver or iron.

3. *Dental Disorders.*—Many investigators have described histological changes which occur in oral structures accompanying vitamin C deficiency in animals.

Therapeutic Uses.—Ascorbic acid is specific for the prophylaxis and treatment of *scurvy.* This effect has been established experimentally and by clinical investigation. Ascorbic acid is of therapeutic value in *early or latent scurvy.* The diagnosis rests on the basis of x-ray evidence in the long bones, the blood level, and possibly failure to excrete an optimum amount of ascorbic acid in the urine. Recommended dosage varies from 100 to 250 mg. two or three times daily by mouth, taken preferably before meals or with meals. Since ascorbic acid is water soluble it may be administered subcutaneously, intramuscularly, or by vein. Relatively smaller doses are indicated than when used orally.

Vitamin C is of therapeutic value in the treatment of *dental caries, pyorrhea, anorexia,* and *undernutrition* when they are the result of a deficiency of this vitamin. Certain *hemorrhagic conditions* and some types of anemia respond to vitamin C therapy. Much evidence has been found for regarding vitamin C as a helpful therapeutic measure in various infections, such as *diphtheria, arthritis, osteomyelitis, pertussis,* and other acute and chronic infections. Despite the vast array of clinical evidence regarding the therapeutic value of vitamin C, there is no absolutely conclusive evidence that ascorbic acid is of value except in the relief of scurvy symptoms.

Much has been written concerning the importance of *vitamin C in wound healing.* Experimental evidence indicates that ascorbic acid is necessary for the formation of collagen fibers and intercellular cement substance. Patients on inadequate diets, as well as those with lesions of the gastrointestinal tract, who are unable to ingest or assimilate food, frequently have low ascorbic acid blood levels. These patients should receive the juice of four oranges and two lemons, or 100 mg. of ascorbic acid, daily.

Administration of Ascorbic Acid.—In planning diets for infants who do not receive breast milk, and for small children, it is advisable to administer ascorbic acid or orange juice, because fresh cow's milk has only one-fourth of the concentration found in mother's milk, and the vitamin in most foods is very sensitive to destruction by oxidation.

If the dietary history discloses a slight lack of vitamin C, dietary adjustment alone may easily rectify the situation. Proper selection of fruits and vegetables can usually increase the intake three or four times. If food fads or other things interfere with the needs or interfere with the use of this vitamin, administer 25, 50, or 100 mg. several times daily. It is rarely necessary to administer it parenterally. Like other water-soluble vitamins it is easily destroyed in the gut if the gastric acidity is low. It is rapidly excreted in the urine, sweat, and diarrheal feces; in such cases administer five to ten times the normal requirement. Attention must be given to the possibility of the washing out of water-soluble vitamins in parenteral fluid therapy. Incorporation of thiamine in the injection mixture is advised.

International Unit of vitamin C represents the vitamin C activity of 0.05 mg. of the international standard crystalline l-ascorbic acid.

A Sherman unit of vitamin C is the daily minimum preventive dose of vitamin C which will prevent a 300 Gm. guinea pig from developing scurvy during a ninety-day period.

Diagnosis of C Hypovitaminosis.—Frank scurvy may be diagnosed on the basis of the history, physical signs, and roentgenologic evidences in the long bones. Mild states of deficiency are frequently difficult to diagnose. The most widely used tests include the urinary excretion of vitamin C, the blood plasma test, and the capillary fragility test. The limits of accuracy of these tests as specific indices of vitamin C nutrition are not yet defined. Estimations on the blood (method of Farmer and Abt, 1936) are probably the more dependable for clinical purposes. Some prefer the determination of the saturation index for estimating the efficiency of vitamin C intake and therapy. *Diet history,* as well as *therapeutic trial,* may be employed to assist in making the diagnosis.

Vitamin C Requirements.—

The Food and Nutrition Board of the National Research Council has recommended the following tentative daily allowances:

For infants (under 1 year)	30 mg.
For children (1 to 20 years)	35 to 100 mg.
Man	75 mg.
Woman (pregnancy and lactation)	100 to 150 mg.
Aged	150 mg. or more

Common Units: One milligram = 20 international units = 2 Sherman units. The U.S.P. Unit of vitamin C is equivalent to the International Unit and represents the activity of 0.05 mg. of U.S.P. Ascorbic Acid Reference Standard.

Preparations are assayed chemically by determining the reducing ability of ascorbic acids. A biologic assay is available based either on prevention or on the cure of scurvy in the guinea pig.

Sources of Vitamin C.—*Dietary:* The best natural sources of vitamin C are oranges, lemons, limes, tomatoes, grapefruit, raw cabbage, turnips, and peppers. The citrus fruits and tomatoes continue to be our chief supply. The content of milk is variable (Bessey, 1938).

Source	*Ascorbic Acid*
Peppers	200 mg. per 100 Gm.
Lemon Juice	60 mg. per 100 Gm.
Spinach	60 mg. per 100 Gm.
Orange Juice	50 mg. per 100 Gm.
Cabbage	40 mg. per 100 Gm.
Tomatoes	30 mg. per 100 Gm.

SPECIAL SOURCES

Ascorbic Acid, *Acidum Ascorbicum,* U.S.P., B.P. *Dosage:* 50 mg. (¾ grain).

Ascorbic Acid Tablets, *Tabellae Acidi Ascorbici,* U.S.P. The usual sizes contain 25 mg., 50 mg., and 100 mg.

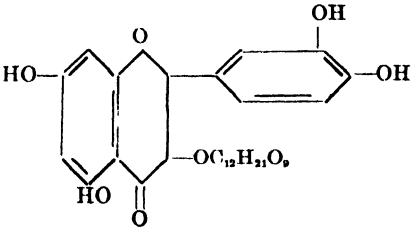
Sodium Ascorbate Injection, *Injectio Sodii Ascorbatis,* U.S.P. Sterile solution of sodium ascorbate in water for injection. *Dosage:* 0.1 Gm. ascorbic acid (U.S.P.) in ampules containing amounts of sodium salt equivalent to amounts of ascorbic acid as 0.1 Gm. or 0.5 Gm. in 2 cc., 0.5 Gm. or 1 Gm. in 5 cc., and 0.5 Gm. in 10 cc.

Citrin (Vitamin P)

A substance distinct from vitamin C has been reported as existing in paprika and lemon rind by Rusznyak and Szent-Györgyi (1936). It consists of two flavone components, hesperidin and demethylated hesperidin, or eriodictin, and has been called "citrin." Citrin is responsible for capillary fragility and some of the symptoms previously associated with scurvy. However, there apparently exists a distinction between the spontaneous hemorrhages of vitamin P deficiency and those associated with low intake of ascorbic acid.

Rutin

Recently, a flavine glucoside, rutin, has been obtained from buckwheat. It is chemically related to hesperidin, a component of vitamin P. It appears sometimes to decrease capillary fragility. The structural formula is as follows:



It is of low toxicity. It is available in the form of small pellets to be taken by mouth, the average dosage being ⅓ grain (20 mg.) three or four times daily. Madison and Pohle (1947) reported that reversion

of erythropermeability had been effected on a high percentage of the cases reported. The therapeutic value of rutin has yet to be demonstrated.

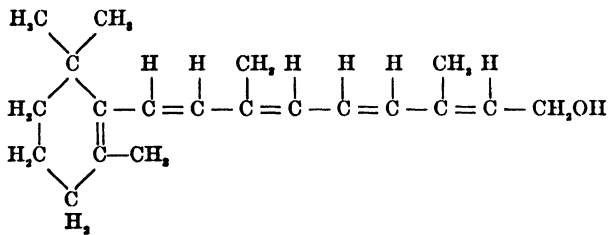
FAT-SOLUBLE VITAMINS

Since vitamins A, D, E, and K are soluble in fats and oils but not in water, they are found only in foods which contain fat or oil.

Vitamin A and Carotene

In 1913, McCollum and Davis, and Osborne and Mendel separately reported observations that certain fats were necessary for normal growth, and the term "Fat-Soluble A" was later given to this essential factor. Since these early experiments, considerable research has been done on vitamin A, with far-reaching results.

The term "vitamin A" has been applied to any one of several substances or to a mixture of them, producing a certain physiologic effect. It has been well established that at least five substances—vitamin A itself, alpha, beta and gamma carotene and cryptoxanthin—can produce to some degree this characteristic response in the animal body. The last four of these are produced in the plant kingdom, and upon ingestion by most animals are transformed into vitamin A. In the body beta carotene breaks down to two molecules of vitamin A. Vitamin A has the following structural formula:



Vitamin A ($C_{20}H_{30}OH$)

Both vitamin A and carotene are extremely sensitive to destruction by oxidation, but in foods are protected by anti-oxidants, hence losses in cooking are not usually great.

Metabolism.—*Metabolism of Carotene.*—Carotene is poorly *absorbed* from raw vegetables but is readily absorbed from solutions in digestible oils. Mineral oil dissolves carotene and hinders the absorption of carotene by the gastrointestinal tract.

Carotene is *stored* in the body fat and in the liver. In the average person about 10 to 20 per cent of the total vitamin A is present as the provitamin carotene. After excessive ingestion of vegetables, some persons store large amounts of carotene in the skin, resulting in a deep yellow color which may be mistaken for jaundice, but has no harmful effect.

METABOLISM OF VITAMIN A.—Vitamin A occurs in foods and liver oils usually combined as an ester with high fatty acids. The ester is saponified before absorption from the intestine. In the absence of pancreatic lipase, i.e., cystic fibrosis of the pancreas, obstruction of pancreatic ducts, little absorption of vitamin occurs. Bile salts are also necessary for the absorption of this vitamin. Defective motility of the jejunum which occurs in vitamin B complex deficiencies, celiac disease and sprue, and giardiasis, interferes with vitamin A absorption.

After drug absorption vitamin A is re-esterified, passes into the portal vein and thoracic duct, and is stored primarily in the liver. The ability of the liver to store vitamin A is decreased in chronic nephritis and liver cirrhosis. Fever hinders absorption of vitamin A and increases its disappearance from the tissues.

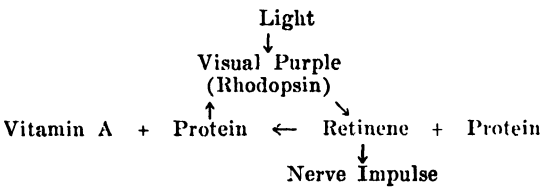
Carotene and vitamin A are normally present in the blood. Concentration of 60 I.U. per 100 cc. in children and 100 I.U. in adults excludes the diagnosis of vitamin A deficiency. Persistent low values in the absence of fever strongly suggest deficiency.

Following excessive doses of this vitamin some may escape in the feces, considerable is eliminated in the milk, and some is lost by destruction. The concentration of vitamin A in milk is proportional to the dietary intake only when the latter is low and reserve in the liver is depleted. When the intake is reduced, the liver stores are utilized before level in the milk is reduced.

Function and Mode of Action.—Vitamin A is seemingly necessary for the proper functioning and structural integrity of the epithelial cells throughout the body. In the absence of vitamin A, epithelial cells atrophy, followed by reparative proliferation on the part of the basal cells, producing a stratified, keratinizing type of epithelium. Since vitamin A enhances the integrity of mucous membranes and epithelial structures, it tends to act as a first line of defense against bacterial invasion of these structures.

A deficiency of vitamin A results in a retardation of growth when body stores of the vitamin are depleted, but bear in mind it assures optimal growth only when all essential nutrients are provided.

Vitamin A is specific for night-blindness or nyctalopia when this condition is due to a deficiency of this vitamin. Cases of nyctalopia, however, due to congenital defects or other diseases than lack of vitamin A will not respond to vitamin A therapy. The following scheme of Wald (1934) is now generally accepted as representing the basic physiological chemistry of dark adaptation, and from it one can readily see the role of vitamin A in the regeneration of visual purple. A depletion of vitamin A retards resynthesis and reduces the available amount of rhodopsin, consequently interfering with visual adaptation.



Clinical Manifestations of Vitamin A Deficiency.—

1. *Eye Lesions: Nyctalopia,* or *night blindness,* is an early symptom of, and constant finding in, vitamin A deficiency. The patient has normal vision in the daytime, but in dim light vision is poor due to failure of the visual mechanism. Vitamin A is a precursor of the visual purple of the retina and in case of deficiency there is a retardation in synthesis of rhodopsin which consequently interferes with visual adaptation. The development of the photometer has made it possible to detect mild grades of vitamin A deficiency in many adults and school children.

Xerophthalmia is another symptom of vitamin A deficiency. This condition, which occurs late in the course of deficiency, is characterized by

keratinization of the cells of the cornea and other structures of the eye. *Xeros,* means dry, and *ophthalmos,* means eye. The name signifies "dry eyes." The conjunctiva appears thickened and the lacrimal glands fail to secrete. This condition is due to keratinization of the epithelium of the glands. In inflammation, processes tend to involve the anterior and posterior chambers of the eye, leading to blindness.

Keratomalacia results from prolonged and severe vitamin A deficiency, the xerophthalmia progressing to a severe degeneration of the cornea, followed by perforation. In most cases permanent blindness is the end result.

2. *Skin diseases* may develop in children due to lack of this vitamin; they are characterized by a dry, scaly skin, by rashes, and by a lowered resistance to skin infections. In adults one of the earliest symptoms is a skin disease known as phrynoderma "toad skin." The sebaceous glands and sweat glands seem to be altered in this condition, with consequent hyposecretion.

3. *Susceptibility to Infections.*—It is difficult to say whether an excess of vitamin A raises the resistance of an individual or whether it exerts a curative effect in respect to infective processes. Some authors (Mellanby and Green, 1929) speak of this vitamin as the antiinfective vitamin, but there is no definite evidence that vitamin A exerts a specific antiinfective function. Mendel states his views as follows: ". . . to stress the indefinite function of the vitamin in preserving 'health and vigor' rather than to herald any specific action against definite microbiotic enemies."

4. The *central nervous system* becomes involved in the presence of avitaminosis A. Mental changes, lack of coordination of movements, weakness of the extremities, and even convulsions have been demonstrated experimentally. Nerve degeneration commences early and progresses simultaneously with other changes. Mellanby (1934) observed degenerative changes in the trigeminal nerves of dogs receiving a diet deficient in vitamin A. There is some evidence that lack of this vitamin may lead to optic neuritis in man. Pathological changes also occur in the *alimentary tract.* The cells of the salivary glands do not function normally, the mucous secretory glands of the intestine become atrophied, and the tips of the villi necrotic. A deficiency of vitamin A may tend to the production of *urinary calculi.* Injury to the female reproductive tract, due to abnormal epithelial growths, may be sufficient to prevent fertilization and implantation of the ovum.

Therapeutic Uses.—Vitamin A is definitely indicated in the treatment of vitamin A deficiency. It is useful in prophylactic treatment during periods of high requirements, such as infancy, pregnancy, and lactation. Once a deficiency is diagnosed 30,000 to 50,000 units of vitamin A are indicated until the desired response is obtained. Vitamin A is reported to be effective in the treatment of certain types of hyperkeratosis of the skin of persons suffering from avitaminosis A.

METABOLIC DISTURBANCES.—Vitamin A frequently is of benefit in metabolic disturbances. It is especially of benefit in diseases when there is faulty absorption, such as in chronic ulcerative colitis, celiac diseases, and diseases of the biliary tract and pancreas. Here massive doses (100,000 to 200,000 units daily) are indicated.

DISEASES OF THE EYE.—In ophthalmologic practice, vitamin A has been suggested for many conditions; the association of xerophthalmia and night blindness with vitamin A deficiency has made ophthalmologists very conscious of the existence of vitamin A. In *xerophthalmia* admin-

ister large doses systemically together with local application of vitamins either as cod liver oil or in an ointment. When *night blindness* is suspected and there is no organic eye disease to account for it, vitamin A deficiency is the most likely diagnosis. Administer large doses of vitamin A (25,000 to 50,000 units daily). Treatment may require several days or several months, depending on the degree of vitamin depletion.

DISEASES OF THE SKIN.—Large doses of vitamin A (100,000 to 300,000 units) are indicated for the treatment of *phrynoderma.* The local use of this vitamin has been reported to accelerate epithelialization in burns and chronic ulcers.

Avitaminosis A is generally considered rare in this country. There are, however, many manifestations of the existence of the milder forms of the disease. The earliest and most reliable evidence of slight vitamin A deficiency is mild hemeralopia or a slightly lowered dark adaptation. A second reliable test consists of making a smear from the light scrapings of the bulbar conjunctiva. When properly stained, the evidence of cornified epithelium indicates a deficiency of vitamin A. In all cases of vitamin A deficiency confirmation of the diagnosis may be obtained by the result of vitamin A therapy; the changes in the eye particularly respond promptly to such treatment. The determination of vitamin A and carotene levels are useful aids in diagnosing vitamin A deficiency.

External Use of Cod Liver Oil.—There is a significant number of clinical reports favorable to the use of cod liver oil ointment in the local treatment of burns, of wounds, and ulcers. Burns in the "indolent stage" and indolent ulcers are said to be especially benefited by local cod liver oil treatment, when dressings are left in place forty-eight hours. It seems evident that local infection diminishes and growth of granulation tissue and epithelization are stimulated. The use of these ointments does not obviate the necessity of recognized surgical principles. Control studies on the benefit of such therapy is woefully lacking.

Diagnosis of Deficiency.—Diet history and symptoms and signs are useful in diagnosing avitaminosis A. Adaptometer tests, blood serum estimations of vitamin A, and carotene are also useful. The therapeutic trial may also be employed.

Vitamin A Requirements.—

Children	6,000 to 8,000 units daily
Adults	3,000 units daily
Women (pregnant and lactating)	5,000 units daily

Common Units: One U.S.P. unit = 1 international unit = the activity of 0.6 microgram of beta-carotene.

The present *U.S.P. assay* is based upon the ability of the vitamin to support growth in vitamin-depleted rats of specified age and weight which are fed a standard diet deficient in vitamin A.

Opinions differ as to whether toxic effects can be produced by feeding massive doses of vitamin A. There is some evidence that pathological conditions follow hypervitaminosis A in experimental animals. Wollback and Bessey (1942) report as follows: "No important change has been seen by us in any of the internal organs. Heart, lungs, liver, kidneys, pancreas, and gastrointestinal tract are essentially normal."

Sources of Vitamin A: *Dietary.*—This vitamin occurs in nature in the following foods: green leafy vegetables, yellow vegetables, liver, eggs, milk, butter, apricots, peaches, oranges, bananas and fish liver oils.

SPECIAL SOURCES

Cod Liver Oil, *Oleum Morrhuae,* U.S.P. It contains in each Gm. at least 850 U.S.P. units of vitamin A and 85 U.S.P. units of vitamin D, with not more than 1 per cent of any official flavoring substance. B.P. must contain a minimum of 600 units of vitamin A per gram. *Dosage:* Infants and adults, 8 cc. (2 fluidrachms), administered one to three times daily.

Non-Destearinated Cod Liver Oil, *Oleum Morrhuae Non-Destearinatum,* U.S.P. Entire fixed oil obtained from fresh cod livers. One gram contains at least 850 U.S.P. units of vitamin A and at least 85 U.S.P. units of vitamin D.

Cod Liver Oil Emulsion, *Emulsum Olei Morrhuae,* U.S.P. Cod liver oil (50%) with acacia, syrup, methyl salicylate and distilled water. Other flavors may be substituted for the methyl salicylate. *Dosage:* Infants and adults, 15 cc. (4 fluidrachms) daily.

Carotene, N.N.R. A solution of carotene (vitamin A) in cottonseed oil in concentration of 7,500 units per Gm.

Shark Liver Oil, N.N.R. An oil extracted from a species of sharks. Contains not less than 16,500 units of vitamin A and not less than 40 units of vitamin D per Gm.

Oleovitamin A, *Oleovitamina A,* U.S.P. (Natural Vitamin A in Oil). Either fish liver oil, or fish liver oil diluted with an edible vegetable oil, or a solution of vitamin A concentrate in fish liver oil, or a solution of vitamin A concentrate in fish liver oil or in an edible vegetable oil. The vitamin A shall be obtained from natural (animal) sources. Oleovitamin A contains in each gram not less than 50,000 and not more than 65,000 U.S.P. units of vitamin A, and not more than 1,000 U.S.P. units of vitamin D. *Dosage:* Prophylactic, infants and adults, 0.1 cc. (1½ minims).

Olevitamin A Capsules, *Capsulae Oleovitaminae A,* U.S.P. *Dosage:* One capsule containing 5,000 U.S.P. vitamin A units.

Oleovitamin A and D, *Oleovitamina A et D,* U.S.P. Contains in each gram not less than 850 and not more than 1,100 U.S.P. units of vitamin A and not less than 85 and not more than 110 U.S.P. units of vitamin D. *Dosage:* Infants and adults, 8 cc. (2 fluidrachms).

Concentrated Oleovitamin A and D, *Oleovitamina A et D Concentrata,* U.S.P. Contains in each gram not less than 50,000 and not more than 65,000 U.S.P. units of vitamin A, and not less than 10,000 and not more than 13,000 U.S.P. units of vitamin D. *Dosage:* Prophylactic, infants and adults, 0.1 cc. (1½ minims).

Concentrated Oleovitamin A and D Capsules, *Capsulae Oleovitaminae A et D Concentratae,* U.S.P. *Dosage:* 1 capsule.

Cod Liver Oil Concentrates, N.N.R. The concentrates obviate certain disadvantages of cod liver oil. They represent the unsaponifiable portion of cod liver oil dissolved in a suitable oily vehicle. They are more expensive than cod liver oil. They are especially adapted to infant feeding, as they contain both vitamins A and D in the same proportion as found in cod liver oil. They are marketed in bottles, vials, capsules, and tablets. They are available in strengths up to 60,000 A units and 8,500 D units per Gm.

Halibut Liver Oil, N.N.R., containing not less than 60,000 A and 600 D units per Gm., may be obtained in bottles and capsules.

Percomorph Liver Oil, N.N.R., with a vitamin content of not less than 60,000 A and 8,500 D units per Gm.

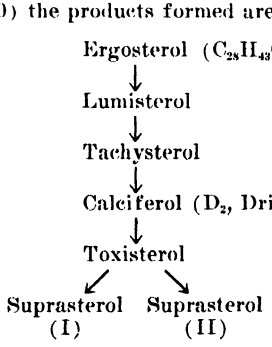
Burbot Liver Oil, N.N.R., is available in capsules, each having a potency of 4,480 A and 640 D units per Gm.

Vitamin D

Although the search for the antirachitic vitamin makes one of the most interesting stories of science, only a few of the major incidents can be mentioned here. As early as 1890 Palm suggested that sunlight possessed an antirachitic action, and in 1919 Mellanby showed that experimental rickets could be prevented by cod liver oil. Huldschinsky (1920) demonstrated the efficiency of sunlight and ultraviolet light in the prevention and cure of rickets. A few years later Steenbock and Black (1924) and Hess and Weinstock (1924), independently, showed that ultraviolet irradiation could impart antirachitic activity to foods. Subsequent studies have led to the chemical identification of vitamin D and its precursors and have enlightened us on the possible mode of action of this important substance.

The term "vitamin D" is applied to two or more substances which have a function in the metabolism of calcium and phosphorus. Of the many substances having vitamin D activity, two are of outstanding importance. They are the products of irradiation of ergosterol and 7-dehydrocholesterol.

Products of Ergosterol Irradiation.—When ergosterol is exposed to irradiation, calciferol is one of the substances formed. According to Windaus (1930) the products formed are as follows:



These compounds are closely related chemically, but possess marked differences physiologically. For example, toxisterol has toxic and calcifying properties greatly disproportionate to antirachitic action. Ergosterol is found in plants, and the activated form, calciferol, is the active constituent in various vitamin preparations such as irradiated yeast, iradiated bread, viosterol, etc.

Ergosterol has no antirachitic effects until irradiated by ultraviolet rays or other means. Irradiation causes an intramolecular rearrangement involving a shift in position of a double bond, the empirical formula remaining the same, $C_{28}H_{43}OH$. *Calciferol* (D_2) is a crystalline substance, and is the international and U.S.P. standard of comparison for viosterol, 1 mg. corresponding to 40,000 units.

Activated 7-dehydrocholesterol.—The irradiation of 7-dehydrocholesterol results in the formation of *activated 7-dehydrocholesterol.* The

irradiation causes an intramolecular rearrangement involving a shift in position of a double bond but not a change in the empirical formula. Cholesterol must first be converted to 7-dehydrocholesterol before it can be converted to the active form. Activated 7-dehydrocholesterol (D_3) is obtained from animal sources and is the form in which the vitamin is found in irradiated milk, and with numerous other antirachitic substances in fish liver oils. This substance is also formed in the skin when exposed to sunlight. For all practical purposes activated 7-dehydrocholesterol (D_3) and calciferol (D_2) have probably equal antirachitic activity in human beings. Vitamin D is commonly employed to mean vitamin D_2 and D_3.

Vitamin D is *absorbed* following oral, subcutaneous, intramuscular, and percutaneous administration. Oral administration is an efficient means of administration. Bile, especially its constituent desoxycholic acid, greatly aids absorption. Approximately 25 per cent of the orally ingested vitamin escapes absorption, the vitamin in the form of cod liver oil is apparently better assimilated than is the more concentrated form. The fate of vitamin D is not known. The vitamin is not rapidly destroyed by the tissues, but is apparently slowly excreted. Vitamin D is excreted in the milk in sufficient amounts to give it appreciable antirachitic value.

Function and Mode of Action.—Vitamin D is an important factor in the regulation of calcium and phosphorus metabolism. The exact mechanism by which vitamin D increases the retention of calcium and phosphorus is not known. Some investigators believe that it aids in the absorption of calcium and phosphorus; others, that it has a local effect on the bones which makes possible proper anchorage or deposition of calcium and phosphorus salts. It is quite possible that both views are correct. Vitamin D would then have a local as well as humoral effect.

Although the antirachitic vitamin is concerned with the prevention of rickets, it is not the specific in the sense that other vitamins are; that is, the absence of vitamin D from the normal diet will not lead to rickets, but if, in addition, the amount or ratio of calcium and phosphorus is abnormal, disorders of bone deposition will occur. The function of vitamin D appears to be to mobilize these calcifying elements, to make possible their utilization even when the diet is inadequate.

In man there are two primary factors in control of calcium and phosphorus: vitamin D associated with absorption of calcium and phosphorus, and the parathyroid gland associated with the mobilization of these elements from the bones.

Clinical Manifestations of Vitamin D Deficiency.—

1. *Rickets.*—Rickets is a common disturbance of infancy and childhood following avitaminosis D. The first symptoms in a child are irritability, fretfulness, and inactivity. At night there is restlessness and excessive sweating about the head and neck. Weakness of the muscles and an apparent inability of the younger child to learn to walk are characteristic symptoms. Digestive disturbances and delayed dentition are common.

Definite confirmatory evidence is obtained by x-ray examination of the long bones and by blood analysis. The x-ray examination shows a failure in calcification of the bone, and a characteristic deviation of the epiphyseal line. The epiphyseal line becomes broad, concave, and irregular, and the end of the diaphysis is broad and ragged. The calcium

content of the blood remains fairly normal, but the inorganic phosphate in the plasma is diminished from the normal of 4 to 5 mg. per 100 cc. to 3.5 to 2.5 mg.

2. *Osteomalacia* is a condition in adults (adult rickets) characterized by deficient calcification and softening of the bones, with consequent deformities. Pathologically and chemically the condition is essentially similar to rickets in children.

3. Vitamin D deficiency also results in *spasmophilia* and *improper tooth formation.*

CLINICAL SIGNIFICANCE: Vitamin D deficiency is apparently uncommon in adults and occurs sporadically mainly as a complication in diseases that interfere with the absorption of food. In the adult no satisfactory clinical test exists. Deficiency of vitamin D is to be suspected when the diet is lacking in the vitamin, or in the presence of such conditions as osteoporosis, osteomalacia, and tetany. It may also be found in pregnancy or lactation, or in diseases that interfere with absorption and utilization of the vitamin, as in celiac disease, jaundice, etc. In suspected cases the effect of vitamin D therapy may be of value diagnostically. In children lack of vitamin D may be readily demonstrated by the presence of characteristic lesions in the long bones, as seen in roentgenograms. Diagnosis of vitamin D deficiency may also be aided by determination of serum calcium, phosphorus, and phosphatase activity.

Therapeutic Uses.—The chief therapeutic indication for vitamin D is in the prevention and treatment of *infantile rickets, spasmophilia,* and *osteomalacia,* diseases which are manifestations of abnormal calcium and phosphorus metabolism. When used for *prevention of rickets,* begin administration at beginning of third week and administer 200 units daily. Increase dosage gradually until by the end of the first month of life 500 to 800 units are given. Vitamin D preparations should be continued throughout period of growth; the dosage, however, may be decreased during the summer months. The curative dose for the treatment of *frank rickets* is approximately 1,200 units, although some cases may require 60,000 units daily. The criteria of cure are a rise in the inorganic phosphorus and x-ray changes showing progressive calcium deposition.

In the treatment of *osteomalacia* large doses of vitamin D in conjunction with a dietary rich in vitamins are indicated.

Scleroderma has been considered the result of faulty calcium metabolism with retention of calcium in the interstitial spaces of the involved area. Vitamin D, 200,000 to 300,000 units daily for several months, has been tried with encouraging results. In *acne vulgaris,* therapy with vitamins has been extensively practiced. Vitamins A, D, and C and pyridoxine are often employed in large doses with some success.

Vitamin D therapy is of value in the treatment of *hypoparathyroidism;* dehydrotachysterol, however, has recently been proved to be of tremendous value in the control of this condition. (See also Hormones.) Since conditions such as diarrhea, steatorrhea, and biliary obstruction would tend to interfere with vitamin D absorption, the prophylactic use of this substance is indicated. Clinical evidence does not warrant the claim that massive doses of vitamin D are of benefit in *allergic disorders, psoriasis,* or *chronic arthritis.* There is no known antirheumatic vitamin. It is true that deficiency of certain vitamins exists not infrequently with chronic arthritis; in such cases vitamin therapy aids the condition by benefiting the general health and not by any "specific" action.

Diagnosis of Deficiency.—The diagnosis of vitamin D deficiency may be made on the basis of the dietary history, symptoms and signs, and by x-ray. Blood serum, calcium, phosphorus and phosphatase determinations are useful in diagnosing avitaminosis D.

Vitamin D Requirements.—

Prophylactic:	800- 1,200 international units daily
Protective:	800- 1,200 international units daily
Curative:	1,200-60,000 international units daily

Common Units: One U.S.P. Unit = 1 international unit = 0.025 microgram of pure crystalline vitamin D_2.

The U.S.P. official method of assay of vitamin D preparations involves the use of rats given a rachitogenic diet. Preparations to be assayed are compared with the standard preparation in regard to their healing effect on the rachitic metaphysis by means of the "line test."

Hypervitaminosis D.—In this condition the calcium and phosphate levels of the blood are raised above normal. Toxic effects may include anorexia, nausea, pallor, lassitude; symptoms suggestive of hypercalcemia may be noted. Poisoning without hypercalcemia may occur. Calcification takes place at an increased rate. When the doses are sufficiently large (1,000 times therapeutic dose), the deposition of minerals at the epiphysis is made at the expense of that in the shaft. Metastatic calcification may occur in the kidneys, blood vessels, heart, stomach, and bronchi. There is evidence of irritation and degeneration in various organs. The animal may lose weight rapidly, have intensive diarrhea, and die in five to fourteen days (Shohl, 1938).

Similar reactions may have occurred in infants given excessive amounts of vitamin D, but it is doubtful (Musser, 1938). Elevation of the serum calcium above 12 mg. per 100 cc. is a danger signal.

In the light of our present knowledge probably none of the vitamins is toxic in excess doses except possibly vitamin D which if administered in excess of 200,000 I.U. per day for an extended period will cause hypercalcemia.

Special Sources

Synthetic Oleovitamin D, Oleovitamina D Synthetica, U.S.P. (Viosterol in Oil [applying only to Activated Ergosterol in Oil]). A solution of activated ergosterol or activated 7-dehydrocholesterol in an edible vegetable oil. Synthetic oleovitamin D contains in each 1 Gm. not less than 10,000 U.S.P. units of vitamin D. Synthetic oleovitamin D must be labeled to indicate whether it contains activated ergosterol *(Vitamin D_2 or Viosterol)* or whether it contains activated 7-dehydrocholesterol (Vitamin D_3). *Dosage:* Prophylactic, 0.1 cc.

Contain Vitamin D and Vitamin A:

Cod Liver Oil.—The official U.S.P., N.F., and B.P. preparations are recommended. Many have already been listed under vitamin A. Other fish liver oils containing vitamins A and D are listed under vitamin A.

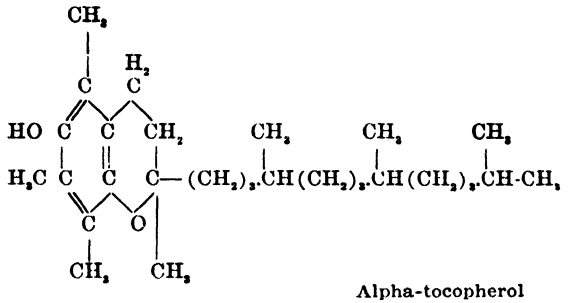
Contain Fish Liver Oils and Irradiated Ergosterol:

Cod Liver Oil With Viosterol, **N.N.R. A preparation of cod liver oil to which has been added irradiated ergosterol (viosterol). Must contain sufficient added ergosterol to raise vitamin D content of the oil to 360 units per gram.**

Halibut Liver Oil With Viosterol, N.N.R. A well-balanced preparation of both vitamins A and D. Total vitamin D content brought to 10,000 units per gram.

Vitamin E

The existence of a dietary factor essential for normal reproduction in the female rat was recognized by Evans and Bishop in 1922. A deficiency of this substance did not interfere with estrus, ovulation, or impregnation of the ovum, but did result in death and resorption of the fetus before the end of gestation. Later (Evans et al., 1936) three related alcohols possessing the biological activity of vitamin E were isolated. To these substances were given the names, alpha, beta, and gamma tocopherol. Alpha-tocopherol, the most active of these compounds, has the following structural formula:



Alpha-tocopherol

Alpha-tocopherol ($C_{29}H_{50}O_2$) is an oily liquid, practically insoluble in water, but soluble in most organic solvents. It should be stored in air-free containers and protected from light and heat. There is little evidence that vitamin E is ever lacking in human diets. Good sources are the vegetable oils from the germs of seeds, such as wheat germ oil, peanut oil, cottonseed oil, etc. Green leaved vegetables, milk and eggs contain significant amounts.

Vitamin E is readily absorbed from the intestinal tract. It is distributed chiefly in fat and skeletal muscles. The animal body can store this vitamin quite effectively.

Function and Mode of Action.—Little is known of the manner in which vitamin E functions in the body. Besides its importance in maintaining pregnancy in the female rat, its deficiency is also accompanied by retardation of growth. Evans and Burr (1928) reported that a characteristic paralysis followed its deficiency in suckling rats. Some workers have reported characteristic central nervous system changes in adult vitamin E-deficient rats. Vitamin E may also affect the level of endocrine functions, particularly the thyrotropic and gonadotropic activities of the pituitary gland.

Another property of vitamin E is its antioxygenic activity, which retards rancidity by interference with the auto-oxidation of fats.

Therapeutic Uses.—Our knowledge of vitamin E is based primarily upon studies conducted on experimental animals. Pregnant females maintained on vitamin E free diet are rendered incapable of retaining the fetus to term. Pathological changes develop in the embryo and in the placenta, resulting in early abortion or resorption of the fetus. Testicular degeneration is a prominent feature of vitamin E deficiency

in male animals, although no change has been observed in the ovaries of the female animal. Spastic paralysis, an associated symptom, is found in both male and female animals. This paralysis is due to degenerative changes that occur in the muscles and connective tissues throughout the body. Growth in young animals is retarded by deficiency of vitamin E.

Experimental observations on animals suggest that vitamin E may be of some value clinically in *abortion, premature labor,* early *separation of the placenta,* and also in the control of *menopausal symptoms* in those patients who either cannot take estrogenic substances or do not show any clinical response to them. Experimental observations on *muscular degeneration* indicate that vitamin E may exert some effect clinically on various types of *muscular dystrophies* and *fibrositis.* Numerous contradictory clinical reports have appeared.

Vitamin E Requirements.—The dosage for alpha-tocopherol has not been established. The biological activity, in rats, of alpha-tocopherol as compared to wheat germ oil may be approximately 100-200 to 1. Daily intramuscular injections of 50 to 100 mg. of alpha-tocopherol solution in oil have been recommended. It may also be administered orally. Larger doses of four to five times this amount may be necessary. At the present time there are no known *contraindications* to its use. Idiosyncrasy to wheat germ oil, however, has been reported. Preparations of vitamin E are not official.

Common Units.—Synthetic alpha-tocopherol acetate ($C_{31}H_{52}O_3$) has been adopted as the international standard.

Special Sources

Wheat germ oil, cottonseed oil, and green leafy vegetables are good sources of vitamin E. Whole cereal grains, legumes, and soy beans also contain vitamin E.

Alpha-tocopherol solution in oil is available for intramuscular administration. It is also available in tablet form; 3 mg. of alpha-tocopherol = approximately 1 cc. of wheat germ oil (unconcentrated). The acetic acid ester of the pure synthetic vitamin E is also available commercially. It is well tolerated and is about 170 times more active than wheat germ oil.

Vitamin K

Of the additions to the therapeutic armamentarium which have been made during the past decade few are of greater interest than the discovery and identification of vitamin K and subsequently the synthesis of its various analogues.

Vitamin K was discovered and named by Dam in 1935, when he observed a hemorrhagic tendency in newly-hatched chicks which could be cured or prevented by the administration of a nonsaponifiable nonsterol fraction of hog liver or alfalfa. Later he observed that the hemorrhagic tendency was due to low prothrombin content.

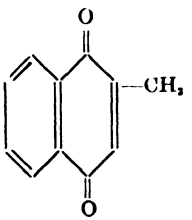
In the meantime Quick had demonstrated that the bleeding tendency long known to exist in obstructive jaundice was also due to a deficiency of prothrombin. Combining these observations with the knowledge that absorption of fat-soluble materials is poor when bile is absent from the intestinal tract, gives the basis for the administration of vitamin K concentrate with bile salts to patients with obstructive jaundice and hemorrhagic tendency.

Sources of Vitamin K.—

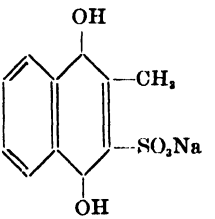
NATURAL SOURCES.—*Extrinsic*—vitamin K may be obtained in the diet from tomatoes, sprouts, green carrot leaves and certain other green-leaved plants. Concentrates for therapeutic use may be obtained from alfalfa leaves. It has been impractical to use these foods effectively in the treatment of hypoprothrombinemic states, presumably because of the low concentration. Mothers have been fed foods rich in vitamin K in abundance without any noticeable elimination of the hypoprothrombinemia of their offspring. *Intrinsic*—another important natural source of vitamin K is the bacterial flora of the gastrointestinal tract. The fact that newborn babies customarily have a low prothrombin level in the blood during the first few days of life is attributed to the absence of bacterial flora.

Vitamin K, the fat-soluble antihemorrhagic substance, is readily absorbed from the intestinal tract in the presence of bile. There is evidence to indicate that only small amounts of vitamin K are stored in the body.

SYNTHETIC SOURCES.—Of great interest and significance has been the discovery that certain synthetic analogues of natural vitamin, particularly 2-methyl-1,4-naphthoquinone (menadione), possesses even greater physiological activity than the natural substance. Certain water-soluble compounds are now available, and may be administered by mouth without bile salts, or parenterally. Some of the water-soluble compounds include—2-methyl-1, 4-naphthohydroquinone-3-sodium-sulfonate, 4-amino-2-methyl-1-naphthol hydrochloride, and 2-methyl-1, 4-naphthohydroquinone diphosphoric ester tetrasodium salt. The following are formulas for a water-insoluble and a water-soluble vitamin K analogue.



2-methyl-1, 4-naphthoquinone
(menadione)
(insoluble in water)



2-methyl-1, 4-naphthohydroquinone-3-sodium sulfonate
(water soluble)

Mode of Action.—The exact role played by vitamin K in the clotting of blood is not yet clearly understood. However, it is apparently essential to the formation of prothrombin, the site of the conversion being the liver. A normal liver can produce prothrombin in the absence of vitamin K. Failure of patients with hypoprothrombinemia to respond to vitamin K therapy is usually traceable to liver pathology.

The hemorrhagic diathesis associated with vitamin K deficiency is characterized by a decrease in level of prothrombin in the blood. Prothrombin is one of the four factors necessary for coagulation—the others being thromboplastin, fibrinogen, and calcium.

Prothrombin + thromboplastin + calcium = thrombin
Thrombin + fibrinogen = fibrin

Menadione, or vitamin K is effective in the prevention and treatment of hypoprothrombinemia and associated hemorrhagic diseases in

newborn infants, in the preoperative and postoperative treatment of patients with obstructive jaundice, and in reducing the tendency to hemorrhage shown by patients suffering from various conditions associated with reduced blood levels of prothrombin.

Hypoprothrombinemia.—Severe cases of hypoprothrombinemia require immediate blood transfusion. In this condition prothrombin is probably reduced to less than 20 or 30 per cent of the normal value.

Less severe hypoprothrombinemia will usually respond quickly to vitamin K therapy unless due to liver disease. Menadione (2-methyl-1, 4-naphthoquinone) may be given orally in doses of 1 to 2 mg. daily, for periods up to four weeks.

In Infants.—Hypoprothrombinemia in the newborn can be corrected by administration of menadione. A single dose of 1 to 2 mg. may be given. Additional administration is gauged by the level of prothrombin achieved.

In pre- and postoperative treatment of *jaundice,* bile salts and menadione should be given for several days before and after operation. The usual dose is from 1 to 2 mg. a day.

Supportive Treatment of Medical Cases.—Menadione may be useful in maintaining the prothrombin concentration in blood when biliary obstruction is due to common duct stricture, duct stone, or adhesions of the bile ducts. It may be useful in biliary fistula, catarrhal jaundice, etc.

Treatment with menadione is of no value in hemophilia, thrombocytopenia, purpura, thrombopenia, aplastic anemia, multiple myeloma, or yellow atrophy of the liver.

No toxic reductions have been observed following therapeutic doses of menadione. Response to therapy should be ascertained by means of prothrombin time determination after twelve, twenty-four, and forty-eight hours, and administration of the drug should be repeated at intervals of one to three days until normal prothrombin levels are attained.

In many instances, parenteral administration is more satisfactory than oral, as the effect is more rapid and absorption more certain. For this purpose, menadione sodium bisulfite may be administered subcutaneously in doses of 2 mg., repeated daily as required.

Method for Determination of Clotting Time.—A simple, roughly quantitative method for the clinical determination of clotting time was devised by Armand J. Quick. (Proc. Soc. Exper. Biol. & Med. 42: 788-789, December, 1939; J. A. M. A. 110: 1658-1662, May 14, 1938.) This test provides a sufficiently accurate criterion of the prothrombin level for most clinical purposes:

> "A drop of blood obtained by a heel or lobe puncture is put on a glass slide, and mixed with a drop of equal size of thromboplastin. The mixture is slowly stirred with a fine pointed stirring rod. By holding the glass slide over a light, the exact clotting time can readily be determined. Normal blood will clot in 15 to 20 seconds.
>
> "Thromboplastin solution: Mix 0.3 Gm. of dehydrated rabbit brain with 5 cc. of physiologic solution of sodium chloride containing 0.1 cc. of sodium oxalate. Incubate at 45° C. for ten minutes, then centrifuge at a slow speed for three minutes to obtain a milky supernatant liquid free from coarse particles."

SPECIAL SOURCES

Menadione, *Menadionum,* U.S.P. (2-Methyl-Naphthoquinone, Menaphthene, Menaphthone). *Dosage:* 1 mg. (1/60 grain).

Menadione Tablets, *Tabellae Menadioni*, U.S.P. Usual size contains 1 mg.

Menadione Sodium Bisulfite, *Menadioni Sodii Bisulfis*, U.S.P. (Menadione Bisulfite). $C_{11}H_8O_2.NaHSO_3.H_2O$. Contains not less than 49 per cent menadione. *Dosage:* Intramuscular or intravenous, 2 mg.; orally, doses not to exceed this amount daily, in tablet form, are usually sufficient. Approximately twice the amount of menadione bisulfite is required to supply an equivalent amount of menadione.

Menadione Sodium Bisulfite Injection, *Injectio Menadioni Sodii Bisulfitis*, U.S.P. *Dosage:* As for menadione sodium bisulfite, making further allowance for the dilution of the compound in solution.

References

Burke, B. S., and Stuart, H. C.: Nutritional Requirements During Pregnancy and Lactation, J. A. M. A. 137: 119, 1948.

Eddy, W. H., and Dolldorf, G.: Avitaminoses, ed. 2, Baltimore, 1941, Williams and Wilkins.

Gorden, E. S., and Sevringhaus, E. L.: Vitamin Therapy in General Practice, Chicago, 1940, The Year Book Pub., Inc.

Gortner, R. A.: Outline of Biochemistry, ed. 2, New York, 1938, John Wiley and Sons.

Guy, R. A.: Vitamins and the General Practitioner, M. Clin. North America 26: 1347 (Sept.), 1942.

Handbook of Nutrition, Chicago, 1943, American Medical Association.

Hawley, Estelle E., and Maurer-Mast, Esther E.: The Fundamentals of Nutrition, Springfield, 1940, Charles C Thomas.

Kleiner, I. S.: Human Biochemistry, St. Louis, 1948, The C. V. Mosby Co.

Krantz, J. C., and Carr, C. J.: Pharmacologic Principles of Medical Practice, Baltimore, 1949, The Williams and Wilkins Co.

McCollum, E. V., Orent-Keiles, Elsa, and Day, H. G.: The Newer Knowledge of Nutrition, ed. 5, New York, 1939, The Macmillan Co.

McLester, J. S.: Nutrition and Diet in Health and Disease, ed. 2, Philadelphia, 1940, W. B. Saunders Co.

Morgan, A. F., and Matill, H. A.: Vitamins in Annual Review of Biochemistry, 1941, Stanford University, Vol. 10.

New and Nonofficial Remedies, 1947.

Proceedings National Nutrition Conference for Defense, May, 1941, U. S. Gov. Print. Office, Washington, D. C., 1942.

Rosenberg, H. R.: Chemistry and Physiology of the Vitamins, New York, 1942, Interscience Publishers.

Spies, T. B., et al.: Some Recent Advances in Vitamin Therapy, J. A. M. A. 115: 292, 1940.

Szent-Györgyi, A. V.: Oxidation, Fermentation, Vitamins, Health and Disease, Baltimore, 1939, Williams and Wilkins.

The Vitamins: A Symposium, J. A. M. A., 1939.

Wolback, S. B., and Bessey, O. A.: Tissue Changes in Vitamin Deficiencies (345 References), Physiol. Rev. 22: 233-289, 1942.

Youmans, J. B.: Nutritional Deficiencies, Diagnosis and Treatment, ed. 2, Philadelphia and London, 1943, J. B. Lippincott Co.

Vitamin A

Bessey, O. H., and Wolback, S. B.: Vitamin A: Physiology and Pathology, J. A. M. A. 110: 2072, 1938.

Booher, L. E.: Vitamin A Requirements, J. A. M. A. 110: 1919, 1938.

Clawson, S. W.: Pharmacology and Therapeutics of Vitamin A, J. A. M. A. 111: 144, 1938.

Moore, T., and Wang, Y. L.: Hypervitaminosis A, Biochem. J. 39: 222, 1945.

Palmer, L. S.: The Chemistry of Vitamin A and Substances Having a Vitamin A Effect, J. A. M. A. 110: 1748, 1938.

Wald, G.: Carotenoids and the Vitamin A Cycle in Vision, Nature 134: 65, 1934.

Vitamin B Complex

Bean, W. B., Spies, T. D., and Vilter, R. W.: A Note on Irradiation Sickness, Am. J. M. Sc. 208: 46, 1944.

Elvehjem, C. A.: The Vitamin B Complex, J. A. M. A. 138: 900, 1948.

Fouts, P. J., et al.: Production of Microcytic Hypochromic Anemia in Puppies on Synthetic Diet Deficient in Rat Antidermatitis Factor (Vitamin B_6), J. Nutrition 16: 197, 1938.

Handler, P.: The Present Status of Nicotinic Acid, Ztschr. f. Vitaminforsch. 19: 394, 1948.

Hogan, A. G.: Riboflavin, J. A. M. A. 110: 1188, 1938.

Joliffe, N., Colbert, C. N., and Joffee, P. M.: Observations on the Etiologic Relationship of Vitamin B (B_1) to Polyneuritis in the Alcohol Addict, Am. J. M. Sc. 191: 515, 1936.

Laws, C. L.: Sensitization to Thiamine Hydrochloride, J. A. M. A. 117: 176, 1941.

Lipmann, F., Kaplan, N. O., Novelli, G. D., Tuttle, L. C., and Guirard, B. M.: Coenzyme E for Acetylation, a Pantothenic Acid Derivative, J. Biol. Chem. 167: 869, 1947.

Minot, G. R., Strauss, M. B., and Cobb, S.: Alcoholic Neuritis, New England J. Med. 208: 1244, 1933.

Munsell, H. E.: Vitamin B_1, J. A. M. A. 111: 927, 1938.

Najjar, V. A., and Holth, L. E., Jr.: The Biosynthesis of Thiamine in Man, J. A. M. A. 123: 683, 1943.

Nelson, E. M.: The Components of Vitamin B Complex, J. A. M. A. 110: 645, 1938.

Oppenheim, A., and Lih, B.: Peroral Administration of Vitamin B_6 (Pyridoxine Hydrochloride) in the Treatment of Radiation Sickness, Radiology 47: 381, 1946.

Reingold, I. M., and Webb, F. R.: Sudden Death Following Intravenous Injection of Thiamine Hydrochloride, J. A. M. A. 130: 491, 1946.

Sherman, H. C., and Lanford, C. S.: Riboflavin Dietary Sources and Requirements, J. A. M. A. 110: 1278, 1938.

Snell, E. E., and Rannefeld, A. N.: The Vitamin Activity of Pyridoxal and Pyridoxamine for Various Organisms, J. Biol. Chem. 157: 475, 1945.

Spies, T. D., Bean, W. B., and Ashe, W. F.: Notes on Use of Vitamin B_6 in Human Nutrition, J. A. M. A. 112: 2414, 1939.

Spies, T. D., Cooper, C., and Blankenhorn, M. A.: The Use of Nicotinic Acid in the Treatment of Pellagra, J. A. M. A. 110: 622, 1938.

Strauss, M. B.: Therapeutic Use of Vitamin B_1 in Polyneuritis and Cardiovascular Conditions, J. A. M. A. 110: 953, 1938.

Sydenstricker, V. P., Geeslin, L. E., Templeton, C. M., and Weaver, J. W.: Riboflavin Deficiency in Human Subjects, J. A. M. A. 113: 1697, 1939.

Williams, R. R., and Spies, T. D.: Vitamin B_1 (Thiamine) and Its Use in Medicine, New York, 1938, The Macmillan Co.

Vitamin C

Bartlett, M. K., Jones, C. M., and Ryan, A. E.: Vitamin C and Wound Healing, New England J. Med. 226: 469, 1942.

Bessey, O. A.: Vitamin C Methods of Assay and Dietary Sources, J. A. M. A. 111: 1290, 1938.

Croft, J. D., and Snorf, L. D.: Vitamin C, Prevalence of Deficiency in Medical Patients, Am. J. M. Sc. 198: 403, 1939.

Farmer, C. J., and Abt, A. F.: Determination of Reduced Ascorbic Acid in Small Amounts of Blood, Proc. Soc. Exper. Biol. & Med. 34: 146, March, 1936.

Hirst, E. L.: The Structure of Ascorbic Acid, J. Soc. Chem. Ind. 52: 221, March, 1933.

Holst, A., and Fröhlich, T.: Experimental Studies Relating to Ship Beriberi and Scurvy. II. On the Etiology of Scurvy, J. Hyg. 7: 634, 1907.

King, C. G.: Physiology of Vitamin C, J. A. M. A. 111: 1458, 1938.

Lind: A Treatise on Scurvy, Sands, London, 1753, Sands, Murray and Cochran.

Smith, S. L.: Human Requirements of Vitamin C, J. A. M. A. 111: 1753, 1938.

Szent-Györgyi, A.: Observations on Function of Peroxidase Systems and Chemistry of Adrenal Cortex; Description of New Carbohydrate Derivative, Biochem. J. 22: 1387, 1928.

Vitamins D, E, K

Bauer, J. M., and Freyberg, R. H.: Vitamin D Intoxication With Metastatic Calcification, J. A. M. A. 130: 1208, 1946.

Bills, C. E.: Physiology of the Sterols Including Vitamin D, Physiol. Rev. 15: 1, 1935.

Blunt, K., and Cowan, R.: Ultra-Violet Light and Vitamin D in Nutrition, Chicago University Press, 1930.

Covey, G. W., and Whitlock, H. W.: Intoxication Resulting From the Administration of Massive Doses of Vitamin D, With Report of Five Cases, Ann. Int. Med. 25: 508, 1946.

Dam, H., et al.: Vitamin K, Skandinav. Arch. f. Physiol. 79: 121, 1938.

Evans, H. M., and Bishop, K. S.: On the Existence of a Hitherto Unrecognized Dietary Factor Essential for Reproduction, Science 56: 650, 1922.

Evans, H. M., and Burr, G. O.: Development of Paralysis in the Suckling Young of Mothers Deprived of Vitamin E, J. Biol. Chem. 76: 273, 1928.

Evans, H. M., Emerson, O. H., and Emerson, Gladys, A.: The Isolation From Wheat Germ Oil of an Alcohol, A-Tocopherol, Having the Properties of Vitamin E, J. Biol. Chem. 113: 319, 1936.

Gaumond, E., and Grandbois, J.: Vitamin D_2 in the Treatment of Lupus Vulgaris, Canad. M. A. J. 56: 205, 1947.

Hess, A. F., and Weinstock, M.: Antirachitic Properties Imparted to Inert Fluids and to Green Vegetables by Ultra-Violet Irradiation, J. Biol. Chem. 62: 301, 1924.

Lozner, E. L., and Kark, Robert: The Therapeutic Use of Vitamin K, M. Clin. North America 25: 1451 (Sept.), 1941.

Mason, K. E.: Physiological Action of Vitamin E and Its Homologues, Vitamins and Hormones 12: 107, 1944.

Mattill, H. A.: Vitamin E, J. A. M. A. 110: 1831, 1938.

Minot, A. S., and Frank, H. E.: Serum Tocopherol—Its Relation to Failure of Vitamin E Therapy for Pseudohypertrophic Muscular Dystrophy, Am. J. Dis. Child. 67: 371, 1944.

Park, E. A.: The Use of Vitamin D Preparations in the Prevention and Treatment of Disease, J. A. M. A. 111: 1179, 1938.

Quick, A. J.: Stanley-Brown, M., and Bancroft, F. W.: Study of the Coagulation Defect in Hemophilia and in Jaundice, Am. J. M. Sc. 190: 501, 1935.

Reed, C. E., Struck, H. C., and Steck, I. E.: Vitamin D, Chicago, 1939, University of Chicago Press.

Shohl, A. T.: Physiology and Pathology of Vitamin D, J. A. M. A. 111: 614, 1938.

Shute, W., and Shute, E.: The Prevention of Premature Labor, J. Obst. & Gynaec. Brit. Emp. 52: 570, 1945.

Smith, H. P., et al.: Clinical and Experimental Studies on Vitamin K, J. A. M. A. 113: 380, 1939.

Stewart, J. D., and Rourke, G. M.: Prothrombin and Vitamin K Therapy, New England J. Med. 221: 403, 1939.

Warner, E. D., and Flynn, J. E.: Absorption of Water-Soluble Vitamin K From Intestinal Tract, Proc. Soc. Exper. Biol. & Med. 44: 607, 1940.

Vitamin P

Griffith, J. I., Jr., Couch, J. F., and Lindauer: Effect of Rutin on Increased Capillary Fragility in Man, Proc. Soc. Exper. Biol. & Med. 55: 228, 1944.

Scarborough, H.: Observations on the Nature of Vitamin P and the Vitamin P Potency of Certain Foodstuffs, Biochem. J. 39: 271, 1945.

CHAPTER XIX

BIOLOGICALS

II. SERUMS AND VACCINES

The subject of serum and vaccine therapy constitutes such an important branch in the field of pharmacology and therapeutics that it is necessary to describe the recognized preparations now in use and their therapeutic applications. Serums and vaccines are employed (1) to indicate susceptibility to disease, (2) to diagnose it, (3) to induce passive or active immunity to it, and (4) to alleviate or cure it.

Many infectious diseases may be prevented and treated by the administration of drugs (biologicals) which combat the invading bacteria or their toxins by building up the immune reaction of the host. These include *sera* which confer passive immunity and *vaccines* which induce active immunity.

Sera include human immune globulin, human measles and scarlet fever immune sera, antibacterial sera, antitoxins, and many more. Vaccines are preparations of attenuated or dead bacteria or viruses, or bacterial toxins or toxoids. They include smallpox, rabies, cholera, plague, typhoid, etc., vaccines; diphtheria, and scarlet fever toxins, and diphtheria and tetanus toxoids. Detailed information on these products may be found in the U.S.P., N.N.R., N.F., and various textbooks.

The general principles of immunity are too complex to permit a lengthy discussion here; on this subject a textbook of immunology should be consulted.

Immunity Reactions.—*Immunity* may be defined as the condition of being immune; security against a particular disease; specifically, the power which a living organism possesses to resist and overcome infection. Immunity may be natural or acquired. *Natural immunity* is the immunity which a person acquires without effort or purpose on his part. It is usually active immunity. *Acquired immunity* is the immunity which an individual acquires after birth. It may be active or passive.

Active Immunity.—*This may be defined as the immunity elaborated by activity of a person's or animal's own tissue, cells, or body fluids.* It may be produced (1) by having and recovering from a disease, e.g., scarlet fever; (2) by the cumulative effect of slight, perhaps unnoticed, infections, e.g., tuberculosis; (3) by inoculation with an attenuated form of the causative organism, e.g., smallpox vaccine; (4) by injection of dead bacteria, e.g., typhoid vaccine; (5) by injection of bacterial products or constituents of the bacterial cell, i.e., as in plague; (6) by injection of toxins, i.e., for production of antitoxin (diphtheria antitoxin); (7) by the injection of other antigens, e.g., red blood cells, tissues (thyroid), blood serum, or other proteins.

The active immunity, formed by the introduction of antigens (toxins, toxoids, tuberculins, and bacterial and viral vaccines), is, in general, slower in appearance but more lasting than the passive immunity caused by introduction of foreign antibodies. It may be secured against many more infections than passive immunity.

Passive Immunity.—*This type of immunity depends upon defensive factors not originating in the individual protected, but is passively acquired by being injected with serum from an individual who has acquired an active immunity against the disease in question.* The effects

of these serums occur immediately on infection, but the protection lasts only a few days or weeks. "Serum sickness," which is due to the injected "foreign" proteins, may occur.

The following sera and vaccines are useful in the prevention, cure and the diagnosis of infecious diseases:

Measles

Human Immune Globulin, U.S.P.
Human Measles Immune Serum, N.F.

Measles, or rubeola, a highly contagious disease, seen mainly in children, is caused by a filtrable virus. Fever, rhinitis, anorexia, vomiting, photophobia, and a maculopapular eruption are the usual symptoms.

Treatment is usually symptomatic, including bed rest, light diet, and plenty of fluids. Human Immune Globulin and Human Measles Immune Serum are used to prevent or attenuate measles.

Complete passive immunization is seldom desirable except in severe outbreaks, since protection lasts only two or three weeks. Partial immunity is preferable as it allows development of an attenuated form of the disease with permanent immunity.

Protection is usually attained by *Human Measles Immune Serum,* N.F. In infants and children of six years or under, administer 10 cc. intramuscularly within five days after exposure. Fifteen cc. are given to children between seven and twelve years of age, 15 cc. are given to older children and adults.

Human Immune Globulin, U.S.P. is useful in the prevention and modification of measles. It is as useful as convalescent serum but has the advantage of being universally available. *Dosage:* Intramuscular for prevention, 2 to 10 cc.; for modification, 2 to 5 cc. (U.S.P.). For modification the injection is made after exposure with the hope of modifying the disease and for the development of active immunity.

Normal Human Serum, U.S.P., and *Citrated Normal Human Plasma,* U.S.P., preparations are used in the treatment of shock and hemorrhage and will be discussed in detail in the next chapter entitled "Blood and Blood Substitutes."

Snake and Spider Bites

Antivenin (Crotalus), N.N.R.
An antitoxic serum prepared by immunizing animals against the venom of snakes of Crotalus family.

Antivenin (Latrodectus Mactans), N.N.R.
An antitoxic serum prepared by immunizing horses against the venom of black widow spider.

In the United States, the copperhead, rattlesnake, and water moccasion are poisonous. Treat by application of tourniquet proximal to bite, incision and intermittent suction (mechanical pump or mouth). Potassium permanganate may be applied to wound. Inject Antivenin (Crotalus) locally in vicinity of bite. The serum may also be given intramuscularly or subcutaneously, and in cases seen late or in very sévère cases give intravenously. Fifty cc. is the minimum dose.

The black widow spider bite is sharp and smarting and is followed in an hour or so by intense local pain and abdominal cramps. Treat with morphine sulfate to allay pain, and, if serious, administer 500 cc. of 10 per cent dextrose solution by vein and 10 cc. or 10 per cent calcium gluconate by muscle. Antivenin (Latrodectus Mactans) may be injected in a dose of 2.5 cc. intramuscularly after an intradermal injection of 0.02 cc. to test for sensitivity.

Botulism

Botulism Antitoxin, N.N.R.

An antitoxic serum prepared by immunizing animals against the toxins of two types of *Clostridium botulinum.*

Botulism is an acute poisoning caused by ingestion of meats, canned vegetables, etc., containing toxins of *Clostridium botulinum.* Treat by lavage of stomach. Give 10,000 units of a potent Botulism Antitoxin at once by vein. Skin tests for sensitivity should be made first. Botulinus antitoxin may be given prophylactically after ingestion of the infected food in a dose of 2,000 units subcutaneously.

Diphtheria

Diphtheria Antitoxin, U.S.P.
Diphtheria Toxin Diagnostic, U.S.P.
Alum Precipitated Diphtheria Toxoid, U.S.P.
Diphtheria Toxin-Antitoxin Mixture, N.N.R.

Diphtheria is an acute infection due to *Corynebacterium diphtheriae* in which there is a membranous pharyngitis and severe toxemia. The primary objective is to neutralize this toxin; and for this purpose *Diphtheria Antitoxin* is the most potent agent known. Administration should be intravenous except in mild cases, when intramuscular injection is permissible. *Dosage:* By parenteral injection: therapeutic, 20,000 units; prophylactic, 1,000 units (U.S.P.).

Prophylactic Treatment.—This is best accomplished by eliminating carriers and actively immunizing all susceptible persons. Carriers should be detected and the infection removed.

Infants should be actively immunized at six months of age and adults when showing a positive Shick test.

The Shick test is performed by injecting 1/40 M.L.D. of Diphtheria Toxin Diagnostic, U.S.P., diluted in 0.2 cc. of physiological saline solution, intracutaneously into the inner side of the forearm. A positive reaction is characterized by a red, raised indurated area.

For immunization Alum Precipitated Diphtheria Toxoid, U.S.P., is most commonly used. Inject 1 cc. of the commercial product subcutaneously. Give Shick test in six months and, if positive, repeat injection of toxoid.

Diphtheria Toxin-Antitoxin Mixture, N.N.R., may be used for active immunization, especially in those who react severely to toxoid, older children, and adults. Ordinarily diphtheria toxoid is preferred. It is given preferably at the insertion of the deltoid, in three doses, with an interval of one week between doses. Give Schick test about six months after last injection. If positive, repeat immunization.

Pertussis

Pertussis Immune Serum, N.N.R.
Pertussis Vaccine, N.N.R.
Pertussis Vaccine and Antitoxin Combined, N.N.R.
Pertussis Vaccine Combined With Diphtheria Toxoid, N.N.R.
Pertussis Vaccine Combined With Diphtheria and Tetanus Toxoids, N.N.R.

Pertussis, or whooping cough, is caused by *Hemophilus pertussis.* Treat the symptoms. Sedatives are indicated for the paroxysms. Probably all infants should be immunized when the diagnosis of pertussis is established. *Pertussis Immune Serum* (Human), N.N.R., may be

administered in dosage of from 5 to 40 cc. (intravenously, given over two days as several injections. Recently, concentrated forms have become available in which 2.5 cc. contain the therapeutic equivalent of 25 cc. One such dose may be given intramuscularly, and repeated again in twenty-four to forty-eight hours if necessary.

Prophylactic Treatment.—Vaccination against pertussis probably is advisable. Immunization is usually started at the age of six months and consists of three injections usually of 1 cc. at monthly intervals. Recent studies indicate that infants seldom possess maternal antibodies against pertussis and that vaccination may be given as early as one week after birth. Vaccines may be combined with tetanus toxoid and diphtheria toxoid, or both, for simultaneous immunization.

Gas Gangrene

Bivalent Gas Gangrene Antitoxin, U.S.P.
Pentavalent Gas Gangrene Antitoxin, U.S.P.
Trivalent Gas Gangrene Antitoxin, U.S.P.
Tetanus and Gas Gangrene Antitoxins, U.S.P.

These preparations are used in the prevention and treatment of gas gangrene. Their value is questionable.

Gas gangrene is caused by wound infection with any of several anaerobes, particularly *Clostridum welchii* and *Cl. oedematis maligni.* Treatment is difficult and requires surgery, chemotherapy, and immunotherapy. Radical removal of infected tissues is indicated. Penicillin, which is our most potent specific agent, should be given in doses of 50,000 units every three hours.

The use of polyvalent gas gangrene antitoxin in severely contaminated injuries greatly lessens the chance of infection. The usual dose is the contents of one syringe (commercial) or even more, this repeated in ten days if necessary.

Tetanus

Tetanus Antitoxin, U.S.P.
Tetanus Toxoid, U.S.P.
Alum Precipitated Tetanus Toxoid, U.S.P.

Tetanus is caused by wound infection with *Clostridium tetani.* Besides quiet and bed rest, nasal oxygen inhalation and parenteral feeding may be necessary. Penicillin may be used to inhibit the organism but it does not neutralize the toxin.

If clinical tetanus (muscle tension, hyperirritability, opisthotonos, and convulsions) has developed, the antitoxin can accomplish little. Administer 50,000 units intravenously to neutralize the toxin in circulation. First, test sensitivity with a small dose. It seems inadvisable to give antitoxin by other routes or in large doses, although both have been advocated by experienced workers.

Prophylactic Treatment.—In case of contaminated wounds, administer 10,000 units intramuscularly; if the wound is extensive, give 20,000 units. A skin test for sensitivity should be carried out and desensitization should be done if positive. Polyvalent serum containing gas gangrene (previous listed) may also be given.

Active immunity may be produced by injection of Tetanus Toxoid or Alum Precipitated Tetanus Toxoid. Administer 0.5 or 1 cc. (correct dosage on package) followed in three months by another dose of equal amount, and thereafter once every two or three years. When wounded, a person treated in this manner need not be given Tetanus Antitoxin but an immediate further dose of toxoid.

Rabies

Rabies Vaccine, U.S.P.
Rabies Vaccine (Semple), N.N.R.
Rabies Vaccine (Pasteur), N.N.R.

Rabies is a disease usually contracted from the bite of a rabid animal whose saliva contains the virus. The usual symptoms are nervousness, inability to swallow, and vomiting. Within a few hours or a day, convulsions and death occur.

Treatment is symptomatic. Sedation is useful to control convulsions. Preventive treatment is the only hope. Clean wounds with water and a local antiseptic. Cauterization of wounds with fuming nitric acid or phenol is advisable.

The animal causing the bite should be caught and observed for two weeks. If the animal remains healthy and the bites are not on the face or hands, vaccine treatment may be delayed. If the animal is not caught, or if he is sick, or if the bite is about the hands or face, start prophylactic treatment at once. Administer injections of Rabies Vaccine on every other day by the intramuscular route. The courses consist of from seven to fourteen injections. Dosage is given on commercial package.

Rabies Vaccine (Semple) is apparently more potent and is used more in this country than Rabies Vaccine (Pasteur).

Brucellosis (Undulant Fever)

Brucella Vaccine, U.S.P.

Brucellosis is caused by one of three species of *Brucella—Br. melitensis, Br. suis,* or *Br. abortus.* The disease usually starts with a severe febrile illness resembling typhoid fever. One-third of the cases pass into a chronic stage characterized by weakness, insomnia, loss of weight, and periodic rises in temperature.

Treatment.—There is no specific treatment suitable for all forms of brucellosis. Treat symptoms as they arise. Sulfonamides are effective in some cases and streptomycin apparently shortens period of acute illness. Vaccine therapy is useful in chronic cases. *Dosage* for Brucella Vaccine: Subcutaneously or intramuscularly, 0.1 to 0.25 cc. of vaccine containing two to six billion killed organisms is the initial dose. Subsequent doses are gradually increased by the amount of the first dose and may be administered at two- to five-day intervals until a dose of 1 cc. is reached.

Cholera

Cholera Vaccine, U.S.P.

Cholera is an acute enteritis, common in Asia, which is caused by the *Vibrio comma.* The infection usually enters the body through the mouth following the drinking of contaminated water. Symptoms include profuse diarrhea and vomiting with resulting dehydration. The mortality is high.

Treatment.—Bed rest and an abundance of fluids are of vital importance. The sulfonamides are moderately effective. Specific antiserums are not particularly effective. *Prevention: Cholera Vaccine* has been used as a prophylactic with some success.

Plague

Plague Vaccine, U.S.P.

Plague is a disease of rodents caused by *Pasteurella pestis.* It is transmitted to man usually by fleas, producing local buboes and septicemia.

Treatment.—Isolate patient and treat symptomatically. Give light diet and force fluids. Streptomycin and also the sulfonamides are of value in some forms.

Prevention by Plague Vaccine appears to be of great value. Persons likely to be exposed should be vaccinated. *Dosage:* Hypodermic for active immunization, 0.5 cc. and 1 cc. with a seven- to ten-day interval, the latter dose to be repeated once (U.S.P.).

Typhoid Fever

Typhoid Vaccine, U.S.P.
Typhoid and Paratyphoid Vaccines, U.S.P.

Typhoid fever is an acute febrile disease caused by *Eberthella typhosa.* It is characterized by general lymphoid hyperplasia, and splenomegaly. Treat symptomatically. No specific therapy is available.

Treatment.—Bed rest and methods to sustain nutrition are important. Immune sera and vaccines are of no avail. Sulfonamide, penicillin, and even streptomycin are of little value.

Prophylactic treatment by vaccination with *Typhoid Vaccine* or *Typhoid and Paratyphoid Vaccines* is advisable. Dosages are given on commercial packages.

Tuberculosis

Old Tuberculin, U.S.P.
Purified Protein Derivative of Tuberculin, U.S.P.
Many Tuberculins listed in N.N.R.

Tuberculosis is a disease caused by *Mycobacterium tuberculosis.* Tissues and organs affected suffer destruction through tubercle formation and allergic reactions, while the host is debilitated by the general toxicity of the process.

Treatment.—There is no specific treatment. Prolonged rest, quiet and proper food are indicated. Prevention of tuberculosis by vaccination has not been successful except with BCG strain. This vaccine is introduced into tuberculosis-negative individuals in whom it is said to initiate a benign, self-limiting process which rather rapidly produces a variable degree of resistance. BCG vaccination apparently has been quite successful in European countries.

The various tuberculins (Old Tuberculin, Purified Protein Derivatives of Tuberculin, and others) are used for the diagnosis of tuberculosis by skin tests.

Scarlet Fever

Scarlet Fever Streptococcus Antitoxin, U.S.P.
Scarlet Fever Streptococcus Antitoxin for Schultz-Charlton Test, N.N.R.
Scarlet Fever Streptococcus Toxin, U.S.P.

There is a tendency to look upon scarlet fever not as a pure disease entity, but as a peculiar reaction of susceptible individuals to some strain of *Streptococcus hemolyticus.* The typical case following an incubation period of three to eight days is characterized by sudden onset with nausea and vomiting, high fever, sore throat, leukocytosis, and with the appearance within twenty-four hours of a scarlet, maculopapular rash on the body and a punctate eruption on the roof of the mouth. The symptoms tend to subside within five to seven days, and a few days after disappearance of the rash the desquamation begins.

Treatment.—Isolation and rest in bed are indicated. Supportive treatment may be necessary. Penicillin has been found superior to the sulfonamides in reducing the toxic state.

Scarlet Fever Streptococcus Antitoxin, 4,000 to 6,000 units, is given intramuscularly. The consensus seems to be that early administration causes subsidence of fever and disappearance of the rash. It may influence the course of the disease. However, there is the likelihood of inducing serum sickness. Convalescent serum, or transfusions from convalescents which furnish the same antitoxin, may also be used. For diagnostic purposes, 0.2 cc. of the antitoxin (Scarlet Fever Streptococcus Antitoxin for Schultz-Charlton Test, N.N.R.) injected intradermally will cause a scarlet fever rash to blanch (Schultz-Charlton reaction).

Prophylaxis: Either passive immunization with Scarlet Fever Antitoxin or active immunization with the toxin is possible, but since these primarily affect the rash rather than serious manifestations of the disease, they are of limited value.

Scarlet Fever Streptococcus Toxin, U.S.P., is used in the Dick test to determine susceptibility to scarlet fever; also for active immunization. For the test to determine susceptibility, inject intracutaneously 0.1 cc. of the dilution representing one skin test dose. A red flare with pseudopodia results when there is no immunity to the toxins of the hemolytic streptococci.

SMALLPOX

Smallpox Vaccine, U.S.P.

Smallpox, or variola, is a virus disease, often epidemic and attended by fever, prostration, and extensive eruption.

Treatment.—Isolation and bed rest are indicated. Treat symptomatically. There are no effective specific measures.

Prophylaxis: Vaccination with *Smallpox Vaccine* ordinarily prevents or greatly modifies the disease even when done several days after exposure. Children should be vaccinated between the ages of six and twelve months and again before six years. Thereafter, vaccination should be done every ten years.

Other Vaccines

Common "Cold" Vaccine.—A number of "cold" vaccines have been developed to prevent the common cold. These preparations consist usually of mixed bacteria often found in the oral cavity, and usually include streptococcus, pneumococcus, staphylococcus, and sometimes *H. influenzae,* Friedlander's bacillus, and *M. catarrhalis.* While the evidence now indicates a viral rather than a bacterial etiology of colds, mixed bacterial vaccines may still be administered by some clinicians on the basis that such vaccines diminish the severity of colds or lessen the severity of secondary infection. Clinical trials indicate that "cold" vaccines actually have little influence on the incidence or severity of colds, nor do they reduce the chances of secondary infection. (Diehl et al., 1940.)

Meningitis Meningococcic Vaccines have been prepared, but prophylactic vaccination does not confer a marked degree of immunity.

Gonorrhea.—A conservative estimate would be that in general the therapeutic use of vaccines in acute gonorrheal conditions has been a failure; in certain cases of chronic infection, for example arthritis, favorable results have been reported.

Staphylococcus Infections.—Vaccine therapy in acute infections is apparently of no value. In the more chronic forms beneficial results may occur.

Influenza Vaccine.—Vaccine made of influenza virus calls forth an antibody response in the recipients, but they do not completely protect against attacks of influenza. The evidence is good that the incidence of the disease is reduced in some groups and that the duration of the disease is shortened.

Rheumatic Fever and Arthritis.—The etiology of these conditions still remains obscure. Different vaccines, however, have been tried, especially from various strains of streptococcus, staphylococcus, and organisms isolated from abscessed teeth, etc. In spite of certain dramatic results it cannot be said that these vaccines have shown impressive therapeutic results. Beneficial and sometimes curative results, however, have followed the use of typhoid vaccine or other vaccines, explained on the basis of nonspecific protein therapy. It is generally the custom to give large doses intravenously to cause a general, though not severe reaction.

Bacterial Vaccines, Mixed.—The employment of vaccines should be based either on the discovery of the causative microorganism or on the established clinical knowledge that the disease was caused by a definite organism. If two or more organisms are associated with the disease, a mixed vaccine may be indicated.

References

Anderson, G. W., and Arnstein, M. G.: Communicable Disease Control, ed. 2, New York, 1947, The Macmillan Co.

Beckman, Harry: Treatment in General Practice, ed. 6, Philadelphia, 1948, W. B. Saunders Co.

Collen, M. F.: Treatment of the Pneumonias, California Med. **66**: 62, 1947.

Cutting, W. C.: Manual of Clinical Therapeutics, ed. 2, Philadelphia, 1948, W. B. Saunders Co.

Diehl, H. S., Baker, A. B., and Cowan, D. W.: Cold Vaccines; A Further Evaluation, J. A. M. A. **115**: 593 (Aug. 24), 1940.

Foshay, L.: Comparative Study of Treatment of Tularemia With Immune Serum, Hyperimmune Serum and Streptomycin, Am. J. Med. Sc. **1**: 180, 1946.

Langley, F. H., and Winkelstein, L. B.: Gas Gangrene, J. A. M. A. **128**: 783, 1945.

Lapin, J. H.: Whooping Cough, Springfield, 1943, Charles C Thomas.

Mackenzie, G. M., and Hanger, F. M.: Serum Disease and Serum Accidents, J. A. M. A. **94**: 260, 1930.

Mackie, T. J., and McCartney, J. E.: An Introduction to Practical Bacteriology, ed. 4, Baltimore, 1934, William Wood & Co.

New and Nonofficial Remedies, 1947.

Ordman, C. W., Jennings, C. G., and Janeway, C. A.: Use of Concentrated Normal Human Serum Gamma Globulin (Human Immune Serum Globulin) in the Prevention and Attenuation of Measles, J. Clin. Investigation **23**: 541, 1944.

Stimson, P. M.: Common Contagious Diseases, ed. 4, Philadelphia, 1947, Lea & Febiger.

Top, F. H.: Communicable Diseases, ed. 2, St. Louis, 1947, The C. V. Mosby Company.

Vinnard, R. T.: 352 Cases of Tetanus, Surgery **18**: 482, 1945.

Zinsser, Hans, and Bayne-Jones, S.: Textbook of Bacteriology, New York, 1939, D. Appleton-Century Co.

CHAPTER XX

BIOLOGICALS

III. BLOOD, BLOOD DERIVATIVES AND SUBSTITUTES

Although blood transfusions were occasionally performed in early times, it is only during the last thirty years that the fundamental principles and technic have been sufficiently established to make it a practical therapeutic measure. Recent studies, fanned by the needs of the military forces in World War II, have developed new and life-saving remedies from common blood.

Definition of Terms.—*Whole blood* may be thought of as essentially a liquid menstruum, called *plasma,* in which are suspended the *formed elements* of the blood, such as red blood cells, white cells, platelets, etc. When withdrawn from the circulation, blood tends to clot because of the presence of *fibrinogen.* If blood is permitted to clot spontaneously, a considerable fraction of liquid may be removed; this is called *serum.* Serum is essentially plasma minus fibrinogen. If blood is prevented from clotting by the addition of some anticoagulant (sodium citrate solution), the liquid portion recovered may be called *citrated plasma* or just *plasma.*

Rationale of Fluid Replacement.—Although divergent views concerning the cause of shock are expressed by various writers, all agree that a marked decrease in the total blood volume is one of the principal factors. This decrease is due in part to loss of blood plasma at the site of injury, to local loss of plasma in burned area, or loss of plasma as the result of increased capillary permeability. This decrease can be best corrected by intravenous administration of whole blood, plasma, or serum. That fluid is indicated for transfusion which most closely resembles that which is lost. Thus in burns, a transfusion of plasma is the logical choice, while in severe hemorrhage, whole blood is indicated.

In the past the indication for transfusion was on the basis of need for red cells, and plasma was rarely considered. *Red blood cells* are of great importance, but they have but one function—that of conveying oxygen from the lungs to the tissue cells. Red cells do not create colloid osmotic pressure or materially increase the effective blood volume or pressure. *Blood plasma or serum* has many functions, not the least important of which is the function of maintaining a colloid osmotic pressure, blood volume, blood pressure, and circulation of red cells. The functions of *blood or its substitutes* may be briefly summarized as follows: (1) Increase in volume of circulating blood, (2) increase in oxygen-carrying capacity of blood, (3) increase in osmotic pressure of blood, (4) increase in blood coagulability, (5) addition of immunologic factors, and (6) possible stimulation of hematopoiesis.

Unfortunately undue publicity has resulted in the widespread but unsound belief that human serum or plasma can be substituted for whole blood in any clinical condition. It is true that serum and plasma may be as efficacious as whole blood in some uses, and even more effective in many others, but remember that whole blood has no substitute in certain conditions.

Whole Blood

There have been many new developments in blood transfusion in recent years—both as to source of blood and method of administration. Most important of these has been the storage of blood for emergency use.

Sources of Blood.—The most common sources of blood are professional or nonprofessional donors, whose blood has been checked for hemoglobin level, cell count, flocculation and grouping, and lack of disease (syphilis, malaria, allergy, etc.). In Russia, cadaver blood has been used extensively. In this country placental blood is of increasing importance as a source of stored blood. However, its use is limited to hospitals possessing a large obstetrical service.

Blood Banks.—The importance of the availability of preserved blood for immediate use needs no emphasis. There is considerable convincing information available which indicates that it is as effective as blood which has recently been drawn.

The following facts are known with reference to preserved blood:

1. Apparently there is no *deterioration* in the plasma proteins for a period of at least sixty days (Scudder, 1940).

2. ***Hemolysis*** of the red blood cells occurs in less than 1 per cent in thirty days, provided a suitable preservative is used. De Gowin and Plass (1940) recommend the following mixture:

Dextrose (5.4%)	13 Volumes, 650 cc.
Sodium Citrate (3.2%)	2 Volumes, 100 cc.
Blood	10 Volumes, 500 cc.
	1,250 cc.

Blood should be stored at temperatures from 0 to 5° C., since hemolysis is greater as temperature rises. Excessive shaking should be avoided.

3. *Leucocytes* disintegrate rather rapidly, that is, within twelve to forty-eight hours, so that old blood has little value in agranulocytosis and also probably in certain cases of sepsis where granulocytes are needed (Kolmer, 1939).

4. *Platelets* agglutinate within twenty-four hours. Therefore, in thrombopenic purpura, old blood is of little value in preventing hemorrhages.

5. *Complement* is active for at least seven to ten days; the bactericidal activity is well preserved for seven days.

6. *Prothrombin* slowly diminishes with storage until it is about 30 per cent of normal in one month. In patients with hemorrhagic diathesis in obstructive jaundice, however, this deficiency can be supplemented by vitamin K.

When blood is to be stored, it is drawn in a citrate solution (sodium citrate 1.2 Gm. in 50 cc. of physiological saline in 500 cc. of blood). Heparin may also be used as an anticoagulant. The blood is then sealed and placed in a refrigerator. Refrigerated blood three to four weeks old has been administered to patients without occurrence of untoward results, but the optimal time for utilization of blood may be placed more safely at two weeks or less after the blood has been put in storage. If stored blood shows any evidence (grossly) of hemolysis or clotting, it should be discarded.

Blood Transfusion.—

(a) *Direct Transfusion.*—The blood is taken from the donor and immediately given to the recipient. Aseptic technic must be followed. If

reactions are thought to be caused by the anticoagulant, this procedure may be useful.

(b) *Indirect Transfusion.*—In giving an indirect transfusion, the blood is placed, observing sterile precautions, into containers containing an anticoagulant and subsequently injected into the recipient.

Because of the flexibility of the *indirect* method of transfusion (citrate or other anticoagulant), it is usually preferred to the direct method. The relative incidence of reaction with the direct method may be slightly less than with the indirect method, but this is more than offset by the practicability of the indirect method. Likewise, since the advent of the use of storage blood, the direct method is less used than it was.

All blood for transfusion should be typed for Landsteiner groups and the Rh factor. Rh-negative males should not receive repeated transfusions of Rh-positive blood and Rh-negative females should never receive Rh-positive blood.

There must also be a record of a negative Wassermann test for the donor. The donors must be free from malaria, infectious jaundice, and possible other transmissible diseases. Allergic reactions may be kept at a minimum if the blood is taken only from fasting donors.

Further information on technic of blood transfusion may be obtained from the authoritative book written by Riddell (1941).

Procedure.—Blood and blood substitutes may be administered, using a 15 gauge Lewisohn needle. Usually thirty to forty-five minutes are allowed for the administration of 500 cc. of blood. Containers are hung fairly high and the rate of drip is regulated by means of a stopcock. When veins are small or poorly filled, venipuncture may be very difficult. Under such circumstances a tourniquet should be placed at a short distance above the site of venipuncture in order to distend the vein to the maximum. Poorly filled veins may be distended satisfactorily by the application of hot moist packs to the extremities, if time permits.

The amount of transfusion required will depend on the patient's needs and response. The patient's blood pressure and pulse should be checked frequently. In severe hemorrhage as much as 2,000 cc. of blood or plasma may be required. The excessive administration of fluid to patients in shock may tend to cause pulmonary edema, excessive strain on the heart, and other ill effects.

Transfusion Reactions.—Blood transfusion is not entirely unattended by untoward effects, and occasionally serious and even fatal results occur. Reactions following plasma infusion are rare. The most serious accidents are usually the result of transfusion with incompatible blood. In such instances the symptoms may consist of anxiety, back pain, and flushing of the face. Death may occur, particularly if the flow of blood is not stopped immediately. Upon appearance of any symptoms of toxicity, the administration of 0.5 to 1.0 cc. of epinephrine (1:1,000) subcutaneously or intramuscularly is indicated.

A chill or fever usually follows initial reactions. This appears to be the result of hemolysis with liberation of free hemoglobin into the blood stream. Whenever a reaction occurs, it is advisable to administer sodium bicarbonate in sufficient amounts to render the urine alkaline. This is done in an attempt to prevent precipitation of hemoglobin in the tubules which may result in obstruction of these passages, causing uremia.

Allergic reactions, such as hives, eosinophilia, and asthma, are sometimes observed. Atropic individuals are undesirable donors since they may confer the same hypersensitivity upon the recipient. Furthermore,

allergic patients may react to substances contained in the donor's blood. It is recommended that the donor be in a fasting condition at the time the blood is given.

Blood Derivatives

Human Plasma and Serum.—The entire field of plasma and serum therapy is new and developing rapidly. New modifications are being constantly made and put into use. Plasma may be preserved in either a wet, dry, or frozen state. The main thing to bear in mind is to use a method that assures a safe, sterile plasma or serum, possessing as many of the original properties of fresh blood as possible.

It is not within the scope of this book to attempt to describe the various methods of preparing plasma or serum. Stringent requirements are established by the National Institute of Health for the manufacture of human plasma and serum.

Plasma vs. Serum.—For a time there was much discussion as to the relative merits of serum and plasma. It appears that, when carefully obtained and prepared, plasma or serum may be equally effective and given with equal safety. Our British and Canadian Colleagues are using serum with highly satisfactory results while opinion in the United States is divided; a majority favor the use of plasma.

Indications.—Citrated human blood plasma is the best substitute for whole blood in wound shock, because typing is unnecessary and it can be preserved for months. If it is dried, it can be preserved indefinitely. Reactions are rare. Pooling of the plasma tends to inactivate harmful substances. Plasma should be filtered before administration to remove any minute particles of fibrin which may block the transfusion needle and, of greater significance, tend to emboli formation.

Citrated Normal Human Plasma, U.S.P., is prepared from the liquid portion of citrated whole blood. It is used in the treatment of surgical and traumatic shock and hemorrhage. It is also used to combat hypoproteinemia in the treatment of burns. The usual dose is 500 cc. by vein.

Serum is used much the same way as plasma. It is free from fibrin. Serum is packaged in liquid form or as the dried powder.

Normal Human Serum, U.S.P., is a sterile serum obtained by pooling equal amounts of the liquid portion of coagulated whole blood from eight or more persons. Its use, dosage, and method of administration are the same as for the Citrated Normal Human Plasma.

Dosage: Plasma is preferably given intravenously, but may be given intramuscularly if the intravenous route is not available. The amount of plasma or serum to be administered varies with the needs of the patient. Although laboratory tests (erythrocytes, hemoglobin, blood protein levels, hematocrit, etc.) are useful, the condition of the patient is the only guide for the amount of material to be employed.

The average dose at one time is 500 cc. However, doses vary from 250 to 1400 cc. Plasma or serum should be administered as frequently as is necessary to meet the needs of the individual patient, it being essential to balance all losses and supply sufficient additional protein to meet metabolic needs.

It should be emphasized that a plasma-treated or albumin-treated shock patient may recover from his shock, but may be an anemic patient. The most serious difficulty resulting from transfusion with whole blood and plasma, especially pooled dried plasma, has been the increasing incidence of *homologous serum jaundice.* Control of this disease is an important medical problem. One approach would be the development of methods of sterilization of blood and plasma.

SERUM ALBUMIN.—Dr. E. J. Cohn, one of America's foremost physiochemists, headed a research group which developed *serum albumin.* This substance is a new blood substitute which does the same job as plasma in treating wound shock. Human serum albumin as prepared contains 25 grams of albumin per 100 cc. of fluid. One-fifth as much albumin is needed for transfusion as when whole plasma is used.

It has the advantage of convenience and compactness, important especially in the Military Service. It does not require refrigeration, and reactions are practically absent.

Blood albumin is useful in shock and low plasma protein. Its chief advantage over plasma is that it can be given in a highly concentrated solution which is of value in patients who may become edematous from excessive volumes of parenteral fluids. The usual dose of a "Unit" of 25 Gm. in 100 cc. of saline, equivalent to 500 cc. of plasma, may be repeated in fifteen to thirty minutes.

More recently serum albumin has been used in *hypoproteinemic edema* and *nephrosis.* Its use in these conditions led to the preparation of a salt-poor albumin solution in which the sodium content is one-seventh that of an osmotically equivalent volume of plasma and in which stabilization has made possible heating at 60° C. for ten hours. This procedure has inactivated the virus of serum jaundice and probably has destroyed many bacteria, making it possible to omit the preservative. Now all albumin produced conforms to the specifications for low salt, preservative-free serum albumin. Serum albumin, of course, lacks oxygen-carrying power, but does not transmit *jaundice* and is easy to handle and administer.

Therapeutic use for albumin is to sustain or restore the level of circulating albumin, in such conditions as severe infections, burns, peritonitis, or abdominal or thoracic operations. Administer large doses, 50 to 100 Gm. in twenty-four hours. A high caloric diet is indicated. In a chronic form of hypo-albuminemia such as nephrosis, the injected protein appears almost quantitatively in the urine and little elevation of serum protein follows daily injections. Nevertheless, adequate doses of albumin (50 Gm. per day for adults) will result in a slow diuresis (Janeway, 1948).

In cirrhosis of the liver adequate doses of albumin (50 Gm. daily) will elevate the serum albumin level. Diuresis and disappearance of ascites may follow in some patients (Kunkle, 1948).

GLOBULINS.—The Harvard group under Dr. Cohn next made a useful study of human blood globulins, another type of proteins. The globulins are those blood proteins which contain important antibodies which fight disease. The object of these studies was to isolate antibodies and use them to protect human beings against disease.

The *measles globulin,* Human Immune Globulin, U.S.P., is an excellent example. It contains the antibodies of the disease in a concentrated form. Measles globulin has been used effectively during the last year and now is being produced on a large scale. Globulin studies are now in progress on other infectious diseases including mumps, scarlet fever, whooping cough, and many more.

Human Immune Globulin is rapidly replacing the use of convalescent serum, pooled adult serum, and placental extract for the passive immunization of certain infectious diseases.

Blood Grouping Globulins.—The anti-A and anti-B agglutinins and the anti-Rh agglutinins can be concentrated and utilized as blood

grouping reagents provided the plasma pool from which they are prepared consists of plasma of a single type (Oncley, 1946).

Recently, favorable results have been reported on the use of bone marrow in aplastic anemia. Large doses of yellow bone marrow are recommended for the treatment of benzol poisoning.

THROMBIN, FIBRINOGEN, AND FIBRIN.—The Harvard group next made a study of both thrombin and fibrin, constituents of plasma. These substances were prepared as purified white powders. When thrombin and fibrinogen unite in solution, they coagulate and form fibrin.

Starting with thrombin and fibrin, films, foams, and glues have been made to be used in surgery. For example, fibrin is used as a substitute for an injured dura, the membrane that covers the brain. The *fibrin film* has been used with notable success to protect injured or destroyed membranes covering the brain. Surgeons wet the film and apply it closely over the wounded areas. Eventually the body replaces the blood fibrin film by its own membrane.

Fibrin foam is an excellent substance to apply to bleeding area to cause blood clotting. It stops bleeding from oozing areas almost immediately. Whether the foam can be supplanted by "Gelfoam" (absorbable gelatin sponge), prepared from gelatin or oxidized cellulose, is difficult to say.

Cellulose-Thrombin. Dr. Tracy Putman of New York's Neurological Center has used oxidized cellulose soaked in thrombin for delicate work in surgery. After operation the substance is completely absorbed by the body.

Fibrin as a Glue. Fibrin is useful in grafting skin to keep it in place, especially in areas about the nose and ears where close proximity is necessary. The surgeon merely sprays fibrin in the wounded area, then applies skin grafts in fibrin solution and fits them in place.

RED BLOOD CELLS.—Even the red blood cells formerly discarded in the preparation of plasma and serum are now utilized. Dr. W. B. Cooksey of Detroit preserved red blood cells in salt solution. He then transfused them into anemic patients and found them as good as whole blood. Now red blood cells are used before and after surgery and to combat a number of diseases including arthritis and tuberculosis.

The cellular components of blood have received much study. Satisfactory methods have been developed for the concentration and preservation of unstable granulocytes and platelets. Considerable effort has been expended to develop suitable methods of preparation of the red cells. Red cell suspensions have two great advantages in the treatment of patients with anemia of all types except those due to acute blood loss or severe infection where there may be a deficit of plasma protein as well. First, they supply more hemoglobin with less of the osmotic activity and with less sodium, thus increasing the dose that can be given safely. Second, the plasma which the patient does not need is saved.

Red blood cells are now used successfully in treating infected wounds, burns, and ulcers. A paste of red cells is applied to the open wound, and healing occurs in a remarkably short time. Now red blood cell preparations which keep indefinitely are available.

Chemical fractionation of red cells has also been accomplished. Preparations of *hemoglobin* in a relatively stable state have been accomplished. Hemoglobin preparations tend to depress the renal function in experimental animals; thus, caution must be exercised in its clinical use.

A derivative of hemoglobin, *modified globin*, has been developed to act as a plasma protein substitute (Strumia, 1945). Further work is necessary before its place in therapy can be evaluated.

Numerous active *enzymes* found in the erythrocyte, such as catalase, choline esterase, hypertensinase, etc., are of interest and may prove of therapeutic value.

Blood Substitutes

SALINE SOLUTIONS.—These are employed intravenously or subcutaneously to restore blood volume and blood pressure in hemorrhage, traumatic shock, burns, and dehydration. In hemorrhage the temporary benefits are often striking, but since the solutions do not stay in the vessels long, other treatment is indicated to save life. The following salines are commonly used for replacing blood and supplying fluid.

PREPARATIONS

Ringer's Solution, *Liquor Ringeri*, U.S.P. (Isotonic Solution of Three Chlorides, U.S.P. XII). Contains in each 100 cc. about 0.86 Gm. of NaCl, about 30 mg. of KCl and about 33 mg. of $CaCl_2.2H_2O$.

Isotonic Sodium Chloride Solution, *Liquor Sodii Chloridi Isotonicus*, U.S.P. (Physiological Sodium Chloride Solution, Physiological Salt Solution, Normal Saline Solution). Sodium chloride (0.9) per cent in water.

Lactated Ringer's Solution, *Liquor Ringeri Lacticus*, U.S.P. Each 100 cc. contains calcium chloride 20 mg., potassium chloride 30 mg., sodium chloride 600 mg., and sodium lactate 310 mg., in sterile distilled water.

Other saline preparations tend to restore blood volume temporarily but are used chiefly for other purposes. Sodium Lactate Injection, U.S.P., is used to combat acidosis of diabetes. It is not indicated in acidosis secondary to congenital heart disease with cyanosis. Sodium bicarbonate may also be administered to correct acidosis. Glucose solutions are occasionally administered to relieve edema but more often to correct ketosis or disturbances in carbohydrate metabolism.

COLLOIDAL SOLUTIONS.—Various colloidal preparations in isotonic saline have been studied as possible agents for transfusions. Colloidal preparations leave the blood vessels slowly and by their osmotic pressure they tend to retain the injected fluid, and thus diminish diuresis, lymph filtration, and edemas. They tend to maintain blood volume longer than do the saline solutions. The colloidal preparations, however, tend to agglutinate red corpuscles, and large quantities are reported to interfere with regeneration of plasma protein (W. Locke, 1944).

Gelatin is used generally as a 6 per cent solution for transfusion. Partial degradation by autoclaving renders it antigenic and less liable to febrile reactions (Cournand et al., 1944).

PECTIN is a complex carbohydrate derived from citrus fruits. One thousand to 1,500 cc. of 1 per cent solution intravenously retain the blood pressure moderately in shock. It leaves the blood stream more rapidly than gelatin. It is nonantigenic and does not alter blood coagulability. It is partially retained in the liver, kidneys, bone marrow, and spleen and produces foreign body reactions and cellular degeneration (Hueper, 1945). Clinical trials indicate that it may be of value as a temporary agent for maintaining blood volume.

Reports covering research done on nutritive, prophylactic, and therapeutic values of the apple suggest that pectin and the uronic acids, as found in the carbohydrates of the apple, together with vitamin A, are valuable substances in the promotion of normal cellular activity of the mucous membrane in the intestinal tract. The uronic acids also have definite value in the detoxification mechanism (I. A. Manville,

1936). Pectin on hydrolysis releases arabinose, galactose, methyl alcohol, and over 90 per cent galacturonic acid. Glycuronic acid, an isomer of galacturonic acid, has long been recognized as a chemical detoxicant, for certain catabolic products and ingested poisons. The action of pectin is well described by Manville, Bradway and McMinis (1937) as follows:

"The physico-chemical value of pectin may be summed up as follows: (1) It possesses great absorptive capacity for bacteria and toxins; (2) because of its colloidal nature it is capable of taking up large quantities of fluid; this provides bulk which helps to sweep out of the intestine harmful materials and to provide a normal stimulus for peristaltic activity; (3) by its buffer action it helps to maintain a constant reaction in the intestine; (4) it acts as a protective colloid to an inflamed and perhaps ulcerated intestinal mucosa."

Pectin-agar mixtures with dextrin and maltose are valuable for the treatment of diarrhea in infants. Pectin, 6.3 per cent, agar, 4.3 per cent, and dextrimaltose, 89.4 per cent, are the ingredients of a preparation which lends well to the making of diets, particularly for infants. The whole effect of this formula may be summarized as follows: (1) pectin retains any value it may have as a detoxicant, adsorbent, and healing agent; (2) it is in a vehicle which promptly controls the diarrhea; (3) the formula results in a high carbohydrate content; a well-tolerated food which tends to combat ketosis and vomiting.

PREPARATIONS

Pectin, *Pectinum*, N.F. Used for emulsifying cod liver oil and in the treatment of diarrhea.

Pectin Paste, *Pasta Pectini*, N.F. Pectin (7.5%), glycerin (18%), benzoic acid (0.2%) in isotonic three chlorides solution.

Thin Pectin Paste, *Pasta Pectini Tenuis*, N.F. Pectin (3.5%), glycerin (7%), benzoic acid (0.2%) in isotonic three chlorides solution.

POLYVINYL ALCOHOL has been tried as a 4 per cent colloidal solution and maintains blood pressure almost as well as blood transfusions. It is retained in the circulation about the same length of time as plasma proteins, and is not retained by the organs (N. W. Roome, 1944).

ACACIA or gum arabic as a 6 per cent solution was widely used in World War I. It leaves the blood stream slowly, beginning soon after injection, being stored largely by the liver, and some by the spleen and kidney. It is believed to cause liver and kidney damage. Benefits from acacia are rather doubtful. Its use has been virtually abandoned.

DEXTRAN, a water-soluble, high molecular polysaccharide, is formed in solutions of sugar inoculated with a special bacterium. Grönwall and Ingelman, 1945, believe this substance to be suitable for infusion fluids.

References

Abbott, W. E.: A Review of the Present Concepts on Fluid Balance, Am. J. M. Sc. 211: 232, 1946.

Bailey, O. T., Ingraham, F. D., Swenson, O., Lowrey, J. J., and Bering, E. A., Jr.: Human Fibrin Foam With Thrombin as a Hemostatic Agent in General Surgery—Experimental Studies and Clinical Use, Surgery 18: 347, 1945.

Brunschwig, A., Nichols, S., and Bigelow, R.: Intravenous Gelatin for Nutritional Purposes—Clinical and Experimental Studies, Surg., Gynec. & Obst. 82: 25, 1946.

Cohen, E. J.: Blood Proteins and Their Therapeutic Value, Science 101: 51, 1945.

Evans, E. I., and Bigger, I. A.: The Rationale of Whole Blood Therapy in Severe Burns, Ann. Surg. **122**: 693, 1945.

Janeway, C. A.: Clinical Use of Blood Derivatives, J. A. M. A. **138**: 859, 1948.

Janeway, C. A., Berenberg, W., and Hutchins, G.: Indications and Uses of Blood, Blood Derivatives and Blood Substitutes, M. Clin. North America **29**: 1069, 1945.

Johnson, J. B., and Newman, L. H.: Intravenous Injection of Acacia-Clinical and Physiologic Effects on Patients With Nephrotic Edema, Arch. Int. Med. **76**: 167, 1945.

Kilduffe, R. A., and DeBakey, Michael: The Blood Bank and the Technique and Therapeutics of Transfusions, St. Louis, 1942, The C. V. Mosby Co.

Kunkel, H. G., Labby, D. H., Abrams, E. H., Jr., Shank, R. E., and Hoaglund, C. L.: The Use of Concentrated Human Serum Albumin in the Treatment of Cirrhosis of the Liver, J. Clin. Investigation **27**: 305, 1948.

McGraw, J. J., Jr., Vaubel, E. K., Reichel, J., Jr., and Elliott, J.: Complications of Blood Transfusion, S. Clin. North America **25**: 1042, 1945.

Moon, V. H.: Shock and Related Capillary Phenomena, New York, 1938, Oxford University Press.

Oncley, J. L., Melin, M., Cameron, J. W., Richert, D. W., and Diamond, L. K.: Methods for the Preparation of Anti-A, Anti-B, and Anti-Rh Isoagglutinin Reagent, Ann. New York Acad. Sc. **46**: 899, 1946.

Popper, H., Volk, B. W., Meyer, K. A., Kozoll, D. O., and Steigmann, F. W.: Evaluation of Pectin and Gelatin Solutions Used in the Treatment of Shock: Histologic Changes Produced in the Human Being, J. Lab. & Clin. Med. **30**: 352, 1945.

Porter, J. E.: Review of the Literature on Blood and Plasma Transfusions (54 references), J. Maine M. A. **32**: 225, 1941.

Riddell, V. H.: Blood Transfusion, New York, 1941, Oxford University Press.

Stead, E. A., Jr., Brannon, E. S., Merrill, A. J., and Warren, J. V.: Concentrated Human Albumin in the Treatment of Shock, Arch. Int. Med. **77**: 564, 1946.

Strumia, M. M., Chornock, F. W., Blake, A. O., and Karr, W. C.: The Use of "Modified Globin" from Human Erythrocytes as a Plasma Substitute, Am. J. M. Sc. **209**: 436, 1945.

Symposium on Plasma, New York State J. Med. **43**: 1601-1618, Sept., 1943.

Unger, L. J., Weinberg, M., and Lefkon, M.: The Rh Factor as Applied to the Operation of Blood Banks, Am. J. Clin. Path. **16**: 498, 1946.

CHAPTER XXI

BIOLOGICALS

IV. HEMATINICS

This chapter includes drugs that influence production of formed elements, agents that affect blood coagulation, and agents that modify the composition of blood in some manner.

IRON AND IRON COMPOUNDS

Iron (ferrum) is a metallic element occurring widely in nature, in both the animal and vegetable kingdoms, and in inorganic compounds. It occurs widely distributed in the body, being found in the chromatin of the cells, in the hemoglobin of the blood, and as a reserve in the blood-forming organs. Iron plays an important role in hemoglobin formation, oxygen transport, tissue respiration, blood-cell development, and hemochromogen synthesis. Deficiency of iron in the body is associated with symptoms of anemia, low vitality, retarded growth, and decreased red cell content and hemoglobin.

Two series of iron compounds exist: the *ferrus,* usually greenish in color, and containing a relatively large proportion of the metal, and *ferric,* generally of a reddish-brown or yellow color. The following forms of iron salts are used in medicine: (1) metallic iron, (2) ferric salts, (3) ferrous salts, (4) inorganic salts, (5) organic salts. The soluble salts have an unpleasant taste, stain the teeth, and often cause stomach irritation, colic, and constipation.

Pharmacological Action.—*Absorption and Excretion.*—*Absorption* of ingested iron, whether in inorganic or organic form, takes place chiefly from the duodenum. It is thought that in the stomach iron is changed to the chloride; next, it combines with protein to form albuminates; then entering the duodenum, it is either taken up by leucocytes or absorbed in solution. It is probable that iron is reduced to the ferrous state before utilization is possible. The old theory that only "organic" compounds of iron could be absorbed by the alimentary tract has been conclusively disproved. The amount permanently absorbed, however, is small, most of the iron ingested passing out with the stools and a large amount being reexcreted into the bowel after absorption. The iron absorbed may later be deposited in the liver and spleen, and iron has been found in bone marrow.

Excretion of absorbed iron takes place slowly through the epithelium of the large intestine. A very small amount is excreted by the kidney. The total amount excreted daily by all channels is estimated at less than 0.0065 gram (1/10 grain).

Normal Iron Retention, Distribution, and Storage.—A positive iron balance is needed in growth, in pregnancy, after hemorrhage, for the formation of hemoglobin and cytochrome. If the intake exceeds the needs, iron is stored in bone marrow, blood, and muscle. Much of it is found loosely bound in the liver and red marrow, and in the spleen and kidneys. In this form it constitutes an important iron reserve which is drawn upon in hemorrhage. Its content is regulated by the amount absorbed rather than by excretion.

Local Action.—Inorganic iron compounds, when taken orally, produce an astringent and irritating effect. Iron acts as an astringent and irritant by reacting with the tissue proteins to form a precipitate of

iron albuminate. If large doses are taken they produce nausea, vomiting, and general weakness, but no symptoms that might be referable to absorption of the iron in the general circulation. Prolonged use of iron may cause constipation and colic due to the constant astringent action on the stomach and bowel. The various forms of "organic" or undissociable iron, and the double salts of iron fail to precipitate tissue proteins, and therefore are nonastringent and are devoid of irritating properties.

General Action.—Orally, iron fails to produce any evidence of general action. Excessive doses cause only gastrointestinal irritation, constipation, and abdominal pain.

Experimentation in animals has shown that the direct action of iron (injection of nonastringent double salts) is manifested by irritation of the nervous system, followed by paralysis. The heart and vessels are little affected. The gastrointestinal tract, however, is irritated; this is shown by a marked swelling and congestion of the mucous membranes of this canal. Vomiting may occur. The kidneys may show signs of irritation and congestion following the administration of small amounts of iron citrate. The respiration is at first elevated by intravenous administration, then becomes slow and labored. Death follows from respiratory paralysis.

Hematopoietic Action.—How iron works in this condition is unknown. It is impossible to suppose that its value is simply a replacement or to supply iron for hemoglobin. The prompt response to large doses of iron in proper cases suggests that it has either a stimulating action on the marrow or an antagonistic effect on blood-destructive processes.

Potentiation of Iron by Copper.—Convincing evidence shows that the addition of copper may be of value in some instances of nutritional anemia in infants (Elvehjem et al., 1937; Usher et al., 1935). Simple nutritional anemias not responding to treatment may be aided by iron and copper therapy (Smith, 1936).

Toxicology.—General intoxication from oral administration of iron preparations is rare (Hurst, 1931). At least four cases of homicidal poisoning are on record. Unfavorable results from the use of iron are usually gastrointestinal irritation, fullness in the head, and occasionally epistaxis or hemorrhage from the throat and lungs. Tachycardia, precordial discomfort, insomnia, and skin eruptions have been attributed to the use of iron. Serious acute poisoning, with such symptoms as pain and paralysis of the extremities, suppression of urine, and even convulsions, is not likely to occur unless iron is given intravenously, as absorption from other routes is too slow to permit general toxic effects.

Certain iron preparations are injurious to the teeth. Morganstern found that ferratin, iron albuminate, reduced iron, and a solution of the saccharate of iron and magnesium had no deleterious action, that ferric citrate exerted a mild caustic effect, and that ferrous sulfate, tincture of ferric chloride, and ferrous lactate caused a more or less marked decalcification and discoloration of the teeth.

Death has been reported from a dose of 1½ ounces of the tincture of iron. A man, aged seventy-two, recovered from the effects of 3 ounces of the tincture (Blyth, 1906).

TREATMENT.—Administer emetics and lavage the stomach with bicarbonates or carbonates. Soap or tannic acid may also be used as an antidote. Injury to the teeth may be avoided by employing noninjurious preparations or by ordering the solution to be taken through a glass tube, or, if a solid preparation, by prescribing it in capsules or gelatin coated pills.

Therapeutic Uses.—*Administration.*—Both organic and inorganic iron are absorbed, but inorganic iron preparations are more active therapeutically. Complex organic preparations are more expensive and may take longer to break down. Soluble ferric salts are more irritant and astringent; this makes the ferrous salt more valuable and suitable for clinical use. Reduced iron is insoluble and should be administered in capsules. Ferric ammonium citrate must be given in large doses and may cause stomach irritation. Ferric pyrophosphate is satisfactory for infants (Elvehjem, 1937). It is practically tasteless and not astringent.

Most hematologists agree that the average daily dose of a preparation of iron should correspond to 1 gram (15 grains) of metallic iron. The daily dose should be administered in three portions; the initial dose should be a small one—0.2 to 0.3 gram (3 to 5 grains) daily—and this amount should be increased until the full amount is administered, or until the patient's tolerance is reached.

Intravenous and intramuscular administration may be indicated to avoid stomach irritation or whenever oral use is contraindicated. Green iron and ammonium citrates were introduced to provide a suitable preparation for intravenous and intramuscular use. Preparations may be obtained in sterile ampules. For administration of iron salts, see Table XXIX.

TABLE XXIX

IRON SALTS FOR ADMINISTRATION BY MOUTH

SALT	DAILY DOSAGE		
	ADULT	CHILDREN	INFANTS TO 4 YR.
Ferrous sulfate	12 grains (0.8 Gm.)	10-12 grains (0.6-0.8 Gm.)	6-8 grains (0.4-0.5 Gm.)
Reduced iron	45 grains (3.0 Gm.)		
Ferrous carbonate (Blaud's pill)	60 grains (4.0 Gm.)		
Ferric ammonium citrate	90 grains (6.0 Gm.)	60-90 grains (4-6 Gm.)	15-45 grains (1-3 Gm.)
Ferric pyrophosphate			2½ grains (0.15 Gm.)

(From Beckman's *Treatment in General Practice.*)

Iron Deficiency Anemia.—The iron-deficiency, hypochronic microcytic anemias are characterized by small pale red cells and a low color index. This condition may result from chronic blood loss, hookworm infestation, excessive blood destruction, malignancy, defective iron absorption, or inadequate iron intake. The basic defect underlying such conditions is a lack of iron. The symptoms caused by iron deficiency anemias are weakness, dyspnea, anorexia, glossitis, and sometimes indigestion and dysphagia. Treatment consists of iron therapy and removal of the cause of the deficiency anemia, if possible.

Iron should always be given orally, unless severe gastrointestinal disturbance renders sufficient absorption from the intestine impossible; then injection is justifiable. The chief cause of failure in the use of iron is inadequate dosage. Twenty to 30 grains of iron a day is

the minimum amount used at present. This would mean 30 Blaud's pills daily or 0.5 gram (7½ grains) of reduced iron three times daily, a total of 1.5 grams (22½ grains). Ferric ammonium citrate is also a favorite form for administration. Dosage: 4 to 6 grams (60 to 90 grains) daily.

In treatment of anemia:

℞

Ferrous Carbonate Pills ---------- No. L.

Sig.: Four to ten pills three times daily after meals.

In treatment of anemia:

℞

Ferric Ammonium Citrate ----------	8.00 Gm.	(3ij)
Potassium Citrate ----------	16.00 Gm.	(3iv)
Cinnamon Water ----------	60.00 cc.	(f℥ij)
Orange Elixir ----------q.s. ad	120.00 cc.	(f℥iv)

M. Sig.: Tablespoonful in water after meals.

For treatment of anemia in children (Elvehjem):

℞

Ferric Pyrophosphate (Sol.)-------	10.00 Gm.	(3iiss)
Cupric Sulfate ----------	0.18 Gm.	(gr.iij)
Alcohol----------	12.00 cc.	(f3iij)
Cinnamon Water ----------	250.00 cc.	(f℥viij)

M. Sig.: One teaspoonful in milk or fruit juice.

HEMORRHAGE.—In hemorrhage iron is indicated. Ferrous carbonates, in the form of Blaud's pills, aid recovery from anemia caused by repeated hemorrhages. In hemorrhages the improvement under iron therapy is slow, and large quantities of iron compounds must be given. The condition responds slowly, as the formed red cell is incapable of synthesizing hemoglobin and the increase must come from newly formed red cells. In severe bleeding infusion is usually indicated. Hemophiliacs, who appear to have an accelerated rate of blood production, are often helped by iron administration.

AS STYPTICS.—Solutions of ferric iron, because of their strong astringent properties, are used externally as styptics. Ferric solutions may be used for their astringent effects internally, and as gargles. Monsel's solution (Liquor Ferri Subsulfatis) and the official aqueous solution of ferric chloride (Liquor Ferri Chloridi) are the preparations of choice. In *gastric hemorrhage,* 0.06 to 0.03 cc. (1 to 5 minims) of Monsel's solution in ice water, and repeated as required, will sometimes give relief. In epistaxis, a weak dilution of Monsel's solution (1:50) may be used in the form of a spray or to moisten cotton pledgets.

IN PREGNANCY AND IN INFANCY.—Routine administration of iron is indicated in pregnancy (Corrigan and Strauss, 1936). Routine administration of iron in infancy is advised by many pediatricians.

OTHER USES.—In *chronic nephritis,* iron in the form of Basham's mixture, Iron and Ammonium Acetate Solution, 8 to 16 cc. (2 to 4 fluidrachms), three or four times daily, has been used. It is used only for treating the *anemia.* A dilute solution of Ferric Sulfate and a mixture of Magnesium Oxide, in 120 cc. (4 fluidounces) dosage, is thought to be of value as an *antidote in arsenic poisoning.* Various iron preparations are used as *tonics.* Iron is also indicated in such conditions as ulcerative colitis, Addison's disease, Banti's disease, erysipelas, lichen planus, scurvy, sprue, and typhoid fever.

In treatment of tonsillitis, etc.:

℞

Potassium Chlorate	8.00 Gm.	(3ij)
Ferric Chlorate Tincture	12.00 cc.	(f3iij)
Sulfuric Acid	15.00 cc.	(f3iv)
Glycerin	24.00 cc.	(f3vj)
Distilled Water q.s. ad	180.00 cc.	(f3vj)

M. Sig.: Tablespoonful in water every four hours.

PREPARATIONS

Ferrous Carbonate Mass, *Massa Ferri Carbonatis,* N.F. Contains $FeCO_3$ (39%) with sugar and honey. *Dosage:* 0.6 Gm. (10 grains).

Ferrous Carbonate Pills, *Pilulae Ferri Carbonatis,* N.F. Each pill contains $FeCO_3$, 0.06 Gm. (1 grain). *Dosage:* 5 pills. *Pilula Ferri Carbonatis,* B.P., 0.3-2 Gm. (5-30 grains).

Ferric Chloride Tincture, *Tinctura Ferri Chloridi,* N.F. Ferric chloride (about 13%) corresponding to not less than 4.5 per cent of iron. *Dosage:* 0.6 cc. (10 minims).

Ferric Ammonium Citrate, *Ferri Ammonii Citras,* U.S.P. (Iron and Ammonium Citrates, U.S.P. XII). Iron citrate rendered more readily soluble by the presence of ammonium citrate. Contains about 17 per cent of iron. *Dosage:* 1 Gm. (15 grains). *Ferri et Ammonii Citras,* B.P. *Dosage:* 5-15 grains.

Ferric Ammonium Citrate Capsules, *Capsulae Ferri et Ammonii Citratis,* U.S.P. (Iron and Ammonium Citrates Capsules, U.S.P. XII). Usual size contains 0.5 Gm.

Green Ferric Ammonium Citrate, *Ferri Ammonii Citras Viridis,* N.F. Equivalent to about 15 per cent iron.

Ferrous Iodide Syrup, *Syrupus Ferri Iodidi,* N.F. Ferrous iodide (FeI_2) (about 7%). *Dosage:* 1 cc. (15 minims). B.P., 5 per cent of FeI_2, 2-8 mils. (30-120 mins.).

Ferrous Sulfate, *Ferri Sulfas,* U.S.P. (Iron Sulfate). *Dosage:* 0.3 Gm. (5 grains). *Ferri Sulphas,* B.P. *Dosage:* 1-5 grains.

Ferrous Sulfate Tablets, *Tabellae Ferri Sulfatis,* U.S.P. Usual size contains 0.3 Gm.

Ferric Subsulfate Solution, *Liquor Ferri Subsulfatis,* N.F. (Monsel's Solution). *Dosage:* Use undiluted.

Reduced Iron, *Ferrum Reductum,* N.F., Metallic iron, Fe (not less than 90 per cent), obtained by reduction of iron oxide by hydrogen. *Dosage:* 0.5 Gm. (7½ grains).

LIVER AND STOMACH PREPARATIONS

Investigations have demonstrated striking effects from the feeding of liver and stomach preparations in hyperchromic, macrocytic anemias, formerly called primary anemias.

Mode of Action.—It is now generally agreed that at least four factors are involved in the formation and utilization of the anti-anemic principle. These factors are: 1. *An Extrinsic Factor.*—Castle (1929) showed that there is a factor in food which supplies the necessary medium with which the gastric juice reacts to form the precursor of the liver principle. The *extrinsic factor* has been found in beef, liver, yeast, wheat germ and, to a lesser extent, in eggs, milk, and tomatoes. It is heat stable, water-soluble, and is extractable from beef or yeast by 65 to 80 per cent alcohol. It is not one or any combination of the known crystalline vitamins.

2. ***The Intrinsic Factor.***—This substance is present in gastric mucosa and secreted in the gastric juice. Castle and his associates showed

that in pernicious anemia there is an inability of the gastric mucosa to secrete this substance. Wilkinson and his co-workers (1938) gave final proof of the presence of this factor. They found that an antianemic substance effective in pernicious anemia was obtained by the incubation of normal human stomachs with beef muscle, but that no such substance appeared in stomachs obtained from patients with pernicious anemia. The *intrinsic factor* in normal gastric juice is heat labile, as are many enzymes. It is destroyed by peptic digestion and is not pepsin, pepsinogen, rennin, or hydrochloric acid.

3. *Interaction Between Extrinsic and Intrinsic Factors.*—Both of the factors are inactive when administered alone but when given together they are highly effective. It is thought that they form an antianemic substance which is absorbed by the intestine. The substance is then carried to the liver, where it is stored and probably further elaborated.

4. *Use of Antianemic Principle.*—The hemopoietic organs utilize the antianemic principle which is stored in the liver for use in building normal blood cells. In pernicious anemia it is thought that the fault lies in the lack of formation of antianemic principle rather than any disturbance in its release or utilization by the bone marrow. It is apparent that the liver principle is essential for all the hemopoietic functions of the bone marrow.

Absorption and Excretion.—The antianemic principle of liver and stomach preparations is *absorbed* from the intestinal tract, rectum and following subcutaneous administration. There is a limited absorption in the intestine, as thirty to fifty times as much liver extract must be given orally as intramuscularly to obtain similar clinical results. Besides being stored in the liver it is also stored in the placenta and is capable of passing to the fetus. It is quite probable that *excretion* occurs through the kidneys.

To avoid the inconvenience of giving large amounts of liver, investigators have searched for effective concentrates. The work of Minot and Murphy, and of Koessler and Mauer, has demonstrated the value of such concentrates. Other investigators have shown that stomach tissues of animals contain a principle capable of stimulating the bone marrow to form immature blood cells (reticulocytes) after its oral administration.

Therapeutic Uses.—Liver and stomach preparations are used in the treatment of *anemias* in which there is defective formation and maturation of red cells. The most important are *pernicious anemia,* in which there is a lack of cell formation, and *tropical sprue,* in which there is impaired absorption and probably lack of an extrinsic or hormone factor. Other conditions characterized by anemia and responding at times to liver therapy include *pellagra, macrocytic tropical anemia, fish tapeworm anemia* and other anemias somewhat resembling pernicious anemia. Liver therapy has been reported to cause improvement in certain cases of atrophic gastritis unassociated with pernicious anemia.

Pernicious anemia and *nutritional macrocytic anemia* are the most common macrocytic anemias. The blood and bone marrow findings are the same. Nutritional macrocytic anemia differs from pernicious anemia in that there is free hydrochloric acid in the gastric secretion; a history of animal protein deficiency in the diet; long standing diarrhea; and in many cases mild or severe exacerbation of pellagra, beriberi, or riboflavin deficiency.

Pernicious Anemia is the most important form of primary anemia. The symptoms include glossitis, achlorhydria, icterus, and, occasionally, combined sclerosis of the spinal cord.

Treatment consists primarily of the administration of liver extracts. If the patient desires an abundant amount of liver in the diet, it is

helpful, although ordinarily reliance is placed largely on concentrated liver preparations.

In severe cases of pernicious anemia, Liver Injection, U.S.P., should be given parenterally as absorption is certain and maximal effects are the rule. Administer 15 U.S.P. Units intramuscularly, daily, for three to seven days. Then administer 15 units weekly for three or four weeks, then only every three or four weeks. Naturally, the dosage should be augmented to the needs of the patient, and the red cell count should never be allowed to fall below the normal value.

If parenteral administration is contraindicated, oral administration may be used, except possibly in cases with nervous system involvement. In the average cases of pernicious anemia 200 to 400 Gm. daily may be adequate. Preparations of powdered stomach may also be used.

Folic acid may be used in this condition. See following paragraphs.

PREPARATIONS

Liver Extract, *Extractum Hepatis*, U.S.P. (Dry Liver Extract). *Dosage:* One U.S.P. unit.

Liver Injection, *Injectio Hepatis*, U.S.P. (Liver Extract for Parenteral Use). *Dosage:* Intramuscular, 1 U.S.P. unit daily.

Liver Solution, *Liquor Hepatis*, U.S.P. (Liquid Liver Extract). Alcoholic content about 19 per cent; glycerin, not more than 40 per cent. *Dosage:* One U.S.P. unit.

Powdered Stomach, *Stomachus Pulveratus*, U.S.P. (Dried Stomach). Dried and powdered defatted wall of the stomach of a hog. *Dosage:* One U.S.P. unit daily.

Liver with Stomach, *Hepar cum Stomacho*, U.S.P. A mixture of mammalian liver with fresh hog stomach tissue. *Dosage:* 1 U.S.P. unit.

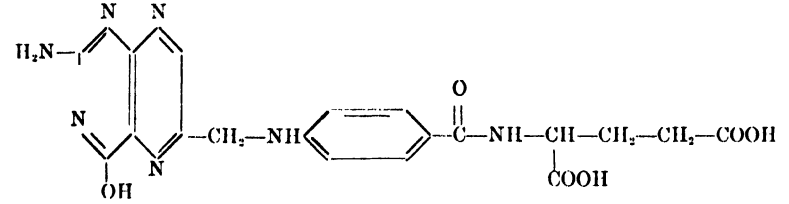
Ventriculin, N.N.R. This is tested clinically for potency and given in doses of 20 to 40 Gm. daily, for initial treatment, and about one-half the dose for maintenance. One gram of the dried material is equivalent to 7 Gm. of the fresh tissue. For oral use.

Extralin, N.N.R. A concentrate from liver and stomach. For oral use.

FOLIC (PTEROYLGLUTAMIC) ACID

Folic acid is a constituent of the B vitamin complex, which has been crystallized and synthesized (Angier, 1946). The therapeutically active form of synthetic folic acid on the market is pteridyl-*para*-aminobenzoyl-glutamic acid.

Folic acid has antianemic actions closely resembling those of liver, but not quite identical. Its advantages lie in its cheapness, its ef-



fectiveness by mouth, and the apparent nondevelopment of sensitivity to it. The relationship of the two is not fully understood. The activity of liver is much greater than its pteroylglutamic acid content. Pteroylglutamic acid is, furthermore, equally potent by mouth and by injection and can be tolerated by persons who are sensitive to liver extract. Folic acid does not appear to be as effective as liver in the treatment of the neuralgic complications in pernicious anemia. It is evidently not the "extrinsic factor" of Castle since it is effective parenterally in low dosage and also in cases in which the intrinsic factor is absent.

Action and Uses.—Folic acid is effective in bringing about a response of the blood similar to that obtained with liver extract in pernicious anemia, sprue, and nutritional macrocytic anemia.

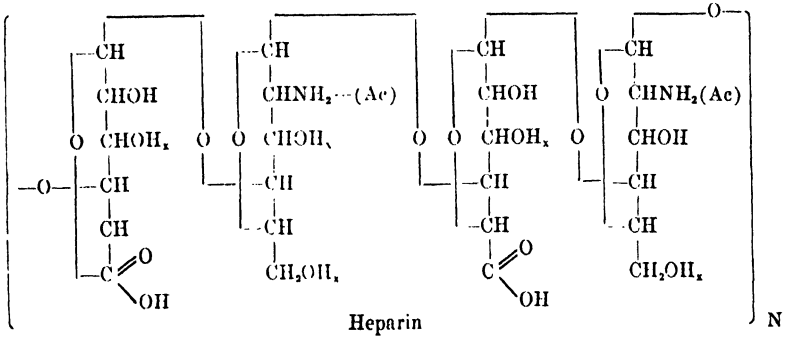
Folic acid controls the diarrhea of sprue, but apparently does not prevent or cause improvement in spinal cord lesions in pernicious anemia; the latter conditions are helped by liver extract. Thus, folic acid may be considered only an adjunct to liver therapy in the treatment of pernicious anemia. *Dosage:* Administer 5 to 10 mg. daily by mouth. It may be administered intramuscularly but this route in ordinary cases is of no advantage.

BLOOD ANTICOAGULANTS

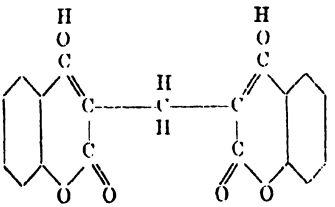
Heparin and Dicoumarin

Heparin

Heparin is a purified liver extract, discovered by McLean (1916), a pupil of Howell, which prevents coagulation of blood. This observation suggested its use in the treatment and prophylaxis of postoperative thrombotic phenomena. As the result of extensive investigations by Best (1933), Jorpes (1935), and others, the heparins have been separated and studied. Structural formulas for heparin and dicoumarin are here shown:



Heparin



Dicoumarin

Pharmacological Action.—*Heparin* may be important in the body for maintaining the blood in the fluid state, although direct proof for such action is lacking. Staining reactions (given by toluidine blue on mucoitin-sulfuric and chondroitin-sulfuric acids) indicate that the content of crude heparin, mast cells, and ester sulfates of various tissues runs parallel to each other. This would indicate that the mast cells produce and secrete heparin.

Mode of Action.—For the role of heparin and the relationship of the other factors in blood coagulation, according to Howell's theory (1918), see diagram discussed under Thromboplastic Substances. Several authors deny the first phase action of heparin. Quick (1936) could demonstrate no antithrombin activity on the part of heparin. In the presence of serum, however, Brinkhous and co-workers (1939) showed that heparin prevented the activation of prothrombin to thrombin.

Heparin prolongs the coagulation time of blood. This is proportional with the quantity in the circulating blood. The action starts at once and is of short duration, due to rapid enzymatic inactivation. See Table XXX.

The contrasting characteristics of dicoumarin and heparin are given us by Prandoni and Wright (1942) in Table XXX.

Therapeutic Uses.—It was demonstrated by Best and his collaborators at Toronto that heparin greatly inhibits the formation of thrombi produced in animals by mechanical or chemical trauma to the intima of large exposed veins. These and similar experiments have stimulated the use of pure heparin in clinical cases of thrombosis and remarkable results have been reported (Jorpes, 1931, Murray, 1940). Heparin has been employed postoperatively with a high degree of success; pulmonary embolism or thrombophlebitis was not observed in instances in which these complications might ordinarily be expected. Swedish clinics (Jorpes, 1939) report striking results in the use of heparin in the treatment of thrombosis of the central vein of the retina and in vascular surgery.

Heparin has been employed successfully in *blood transfusions.* It may be substituted for citrate, may be used in solution in syringes and tubing, or for heparinization of the donor. See reports of Hedenuis (1936), Sappington (1939) and others. Reports indicate that heparin may be of value in the treatment of *subacute bacterial endocarditis.* It is administered in an attempt to prevent further thrombotic deposition of fibrin and platelets on the surfaces of the valves of the heart. Heparin combined with the sulfa drugs offers some promise in this disease.

Administration.—There are essentially only two methods that are useful in treating hospital patients. (1) The *continuous intravenous drip method* and (2) the *injection of heparin solutions every two or three hours.* Crafoord (1941) treats most of his patients by this latter method, giving about 50 mg. (approx. 5,000 units) every two hours, for four to five days postoperatively. By this method the clotting time is raised quickly from a normal of four or five minutes to from fifteen to twenty-eight minutes. Two hours after the injection the clotting time has usually returned to normal.

In this country and Canada the following plan is usually employed: Just before continuous administration of heparin solution the patient is given 5 cc. of undiluted heparin solution, i.e., about 5,000 units, intravenously. This amount of heparin will quickly raise the clotting time to fifteen or twenty minutes. Then diluted heparin solution is given the patient by continuous intravenous drip at from fifteen to

TABLE XXX

CONTRASTING CHARACTERISTICS OF DICOUMARIN AND HEPARIN*

	DICOUMARIN	HEPARIN
Chemical classification	3,3'-Methylene-*bis*-(4-hydroxycoumarin)	Mucoitin polysulfuric acid
Preparation	1. Extraction from spoiled sweet clover hay 2. Synthesis	Extraction from blood, liver, lung, and other tissues Commercially, it is prepared from lung and liver
Effect manifested by	1. Prolongation of prothrombin and coagulation times	1. Inhibition of platelet agglutination 2. Prolongation of coagulation time
Effect antagonized by	1. Fresh whole blood	1. Trypsin 2. Thrombokinase 3. Snake venom 4. Salmine sulfuric acid
Dose	Variable (approximately 300 mg. on alternate days in recent cases has proved satisfactory)	Variable (approximately 20-mg./kg.)
Method of administration	1. Oral 2. Intravenous	Intravenous (continuous drip, multiple divided dose)
Initial response occurs	24-72 hours	Immediately
Duration of effect	2-26 days; average 11.2 days	1-4 hours
Hemorrhagic manifestations	Purpura, ecchymoses, hematuria, gingival hemorrhage, epistaxis, conjunctival hemorrhage	Hematomas, hematuria, cerebral hemorrhage
Hemorrhagic tendency controlled by	Transfusions of fresh whole blood or plasma	1. Salmine sulfuric acid 2. Blood transfusion

*Reprinted from Bull. New York Acad. Med. 18: 433, 1942.

twenty-five drops per minute. The patient usually requires from 1,000 to 1,500 units per hour the first or second day, after which 500 to 1,000 units per hour are sufficient. The clotting time should be checked at least three times daily. Toluidine blue may be used to stop the bleeding tendency in a patient given too much heparin (Holoubek, 1949).

Units and Dosage.—The original Howell unit is the amount of heparin which will prevent the clotting of 1 cc. of cat's blood for

twenty-four hours when kept at 0° C. Murray and Best later proposed as a unit the equivalent of $\frac{1}{100}$ mg. of crystalline barium salt of heparin. The required dosage for heparin varies considerably with each patient. An average dose may be approximately 750 to 1,000 units (Toronto preparation) per hour. *Toxic reactions* were common with earlier preparations of heparin, but the purified heparin that is available at the present time is nontoxic when given intravenously.

DICOUMARIN

A most interesting development in the field of biologic research has been the recognition, isolation, and finally, synthesis of the substance causing hemorrhagic sweet clover disease in cattle, dicoumarin, (3,3'-methylene-*bis*-4-hydroxycoumarin). Schofield (1922) and Roderick (1931) studied and quite accurately analyzed the factors responsible for this phenomena in cattle and rabbits. In a series of brilliant reports, beginning in 1940, Campbell and Link and their co-workers established that the hemorrhagic agent was a dicoumarin and succeeded in isolating, crystallizing, and synthesizing the active substance. Meyer, Bingham and Pohle (1941) presented the first report on the action of dicoumarin in man. Other workers including Allen, Barker and Waugh (1942); Wright and Prandoni (1942); Bollman and Preston (1942), and others, have contributed valuable investigations toward the clinical use of dicoumarin. It must, however, be borne in mind that the therapeutic value of dicoumarin has not yet been clearly established. At present, however, three advantages over heparin are apparent: (1) effective orally, (2) prolonged action, and (3) cheapness. It appears likely that the use of dicoumarin may well replace the clinical use of heparin and probably may have even certain advantages over heparin.

Like heparin, dicoumarin is capable of greatly reducing the incidence and degree of experimental thrombus formation (Meyer et al., 1942). Experimental animals receiving the drug showed some histologic signs of damage to liver parenchyma. However, liver function tests (glucose tolerance and B.S.P. retention) failed to show any change in liver activity.

Unlike heparin, dicoumarin prevents coagulation in vivo, but not in vitro. Also, its action is not manifested until at least twenty-four hours after administration. (See Table XXX.) A considerable period of time intervenes between the cessation of dicoumarin medication and the return of the normal coagulability of the blood, whereas in heparin therapy the response is almost immediate.

Although most of the study done on dicoumarin has been devoted to the mechanism and pharmacological action of dicoumarin, it is expected that much of the future work will be primarily upon therapeutic considerations.

Certain salient facts concerning dicoumarin are listed:

1. Dicoumarin should be administered only when guided by repeated calculations of prothrombin time.
2. The effect on prothrombin time is proportional to amount of dicoumarin administered. Individual variations are found.
3. The oral administration prolongs prothrombin time, impairs clot retraction, and increases the sedimentation rate of erythrocytes.
4. Synthetic vitamin K has little or no effect on prolongation of prothrombin time resulting from dicoumarin.
5. The danger of hemorrhage from dicoumarin therapy serves as a constant emphasis for care in its use.

6. The action of heparin is not prolonged when given to dicoumarinized animals and heparin is not involved in the action of dicoumarin.
7. Sulfathiazole therapy has no effect on the effectiveness of dicoumarin.
8. Dicoumarin in proper dosage is apparently nontoxic.

Dicoumarin Therapy.—Dicoumarin may be administered by mouth or intravenously. Various plans have been found effective. Wright and Prandoni found the following dosage plan useful:

Dosage: 300 mg. on first day
200 mg. on second day
200 mg. on each following day on which prothrombin time is less than thirty-five seconds. Check prothrombin time (see "Bedside Test" under vitamin K) every twenty-four hours. Response to first dose may be expected in twenty-four to forty-eight hours. After discontinuing dicoumarin, the prothrombin time may be prolonged from two days to two or three weeks, depending on the dosage. Its effect should be maintained for at least four weeks.

Heparin and dicoumarin may be administered together when both quick and prolonged action are desired. The use of heparin may be discontinued when the prothrombin time has been satisfactorily prolonged by dicoumarin. The combination of these two drugs produces no incompatibility. Constant emphasis must be placed on the danger of hemorrhage. In case of hemorrhage inject 65 mg. of menadione sodium bisulfite. Transfusions of fresh whole blood or plasma may be indicated.

INDICATIONS FOR DICOUMARIN:

1. Dicoumarin is valuable in the treatment of *thrombosis* and *embolism.* Its effect should be maintained for at least four weeks.
2. Dicoumarin may be used for the treatment of all cases for which heparin is advocated.

CONTRAINDICATIONS:

1. Dicoumarin should be used with caution, or not at all, in cases associated with ulcerating lesions.
2. Dicoumarin should not be used in bleeding patients.
3. It should not be used in cases in which the prothrombin time is already prolonged (vitamin K deficiency).
4. Subacute bacterial endocarditis, renal and hepatic insufficiency.

BLOOD COAGULANTS

Agents which promote blood coagulation include vitamin K, thrombin and thromboplastic tissue extracts, and many more. Toluidine blue and protamine sulfate are useful in certain types of bleeding.

Vitamin K preparations prevent hemorrhages by raising the prothrombin level of the blood. For discusion see chapter on Vitamins.

Thrombin is prepared commercially from bovine plasma, by the conversion of prothrombin with thromboplastin. It is used as a hemostatic for topical application to control bleeding in operative procedures. It may be applied as a dry powder or in isotonic saline solution. *Do not inject.*

Thromboplastic Substances.—Preparations containing thromboplastin were originally prepared by Howell by extracting ox brain. They are believed to be composed of a protein and a phospholipid. When applied to oozing surfaces they tend to prevent bleeding. They should not be

injected. Thromboplastic substances are not used extensively in surgery. Brain Lipoid, N.N.R., is an extract of ox brain for local application to oozing surfaces. Solution Brain Extract, N.N.R., is an extract of cattle brain in isotonic solution of sodium chloride prepared for local application to prevent bleeding.

Toluidine Blue.—The use of toluidine blue as an aid in controlling the general tendency to bleed in thrombocytopenia was suggested by Allen in 1947. More recently Holoubek et al. (1949) reported toluidine blue as a valuable adjunct in the treatment of petechial bleeding. Doses varying from 1 to 3 mg. of toluidine blue were administered daily.

It was felt that the action of toluidine blue or protamine sulfate was due to the ability of these substances to render heparin inactive. The so-called antiheparin drugs, i.e., toluidine blue, protamine sulfate, are valuable drugs in the treatment of petechial bleeding with thrombopenia in properly selected cases. They are also useful antidotes for patients given too much heparin.

SCLEROSING AGENTS

Sclerosing agents are used to produce thrombosis and obliteration of veins, especially varicose veins and hemorrhoids. Solutions of ethyl alcohol, invert sugar, iodides, iron salts, mercuric chloride, phenol, quinine and urea, quinine and urethan hydrochloride, sodium morrhuate, sodium citrate, and others have been employed. Quinine and urethane and sodium morrhuate will be described.

Sodium Morrhuate

Sodium morrhuate is used extensively for sclerosing purposes. A sterile solution of the sodium salts of the fatty acids of cod liver oil is injected intravenously to cause sclerosis, thrombosis, and obliteration of veins.

Varicose Veins.—Small isolated varicosities may be thrombosed by injection of 0.5 cc. of 5 per cent sodium morrhuate solution. More extensive involvement requires ligation of the greater saphenous vein at the saphenofemoral junction, and injection of 0.5 to 3 cc. of sodium morrhuate into the distal end of the vein. It causes little pain on injection. Most Council-accepted preparations (1947) contain 2 or 3 per cent of benzyl alcohol as a local anesthetic.

Quinine Dehydrochloride and Urethane

A mixture of quinine dehydrochloride and urethane in aqueous solution is used as a sclerosing agent. The initial injection should be limited to 0.5 cc. to test for hypersensitivity. The average amount of injection at any one site is 1 cc. and should not exceed 2 cc. of Quinine and Urethane Injection, U.S.P. Make injection slowly. It should not be employed during menstruation, pregnancy, nor in the presence of heart disease, nephritis, diabetes, upper respiratory infection, or toxic tonsillitis. It is contraindicated in the presence of phlebitis, suppurative ulceration, and incompetence of deep veins.

Preparations

Sodium Morrhuate Injection, *Injectio Sodii Morrhuatis*, U.S.P. *Dosage:* To be determined by the physician according to the needs of the patient (U.S.P.).

Quinine and Urethane Injection, Injectio Quininae et Urethani, U.S.P. (Quinine Hydrochloride and Ethyl Carbamate Injection, U.S.P. XII). A sterile solution in water for injection of approximately two parts quinine hydrochloride and one part urethane. The usual size contains 0.25 Gm. quinine hydrochloride and 0.12 Gm. urethane in 2 cc.

PENTNUCLEOTIDE

Pentnucleotide, N.N.R., is the sodium salts of pentose nucleotides from ribonucleic acid of yeast. It is indicated in infectious conditions accompanied by leukopenia or neutropenia such as agranulocytosis.

Agranulocytosis.—The continued administration of certain drugs (aminopyrine, acetanilid, dinitrophenol, cinchophen, and many more) may result in a decrease in the number of white blood cells, especially those of the granulocyte series. Fever, prostration, and secondary infection are seen clinically. Some clinicians (Fisher, et al., 1946) recommend 10 cc. intramuscularly every six hours. Agranulocytosis in patients seen by Timmes (1946) in Nagasaki, following discharge of the atom bomb, were given 3 cc. dosages three times daily and it was reported that a rise in white blood cells appeared in twenty-four hours. In general, Pentnucleotide is used mostly with uncertain results in this condition.

The successful employment of penicillin and streptomycin should not be lost sight of. They are the drugs of choice. See Penicillin and Streptomycin.

RADIATION THERAPY

Radiation therapy was introduced about a half century ago for the treatment of blood dyscrasias. It has definite value in such conditions as polycythemia vera, chronic leukemias, lymphosarcoma, Hodgkin's disease, multiple myeloma, and other conditions.

In *polycythemia vera* roentgen irradiation of the long bones, or the whole body, is effective in decreasing the red cell count, as the depressed bone marrow produces fewer cells. Effective irradiation may also be furnished by intravenous injection of radioactive phosphorus.

The effects of radiation therapy are only palliative, mainly relieving pain and pressure symptoms. The treatment may be given at frequent short intervals, or intensive treatment may be initiated. The whole blood cell count must be followed carefully since leukopenia may result from excessive treatment. Toxic symptoms may result from radiation therapy including anorexia, nausea, and vomiting. Excessive doses may cause severe hemorrhages.

RADIOACTIVE PHOSPHORUS

Lawrence, et al., 1939, introduced radioactive phosphorus for the treatment of blood diseases. It may be administered orally or intravenously, preferably the latter. Following administration it is concentrated in rapidly growing tissues, especially those high in phosphorus content.

Radioactive phosphorus is possibly the treatment of choice for polycythemia vera. It slows the rate of red cell formation and improves the patient physically. The usual single dose of P. 32 is one millicurie; a course of treatment is usually three to seven such doses. In polycythemia vera, up to 15 millicuries may be indicated. Its use, however, is only palliative, as it does not cure the condition.

Radioactive phosphorus does not cause radiation sickness. Its use is relatively free from long-range harmful effects. Leukopenia, thrombocytopenia, and anemia may follow its use, due to depressant action on bone marrow. Its penetrating powers are limited, yet for all practical purposes its action is of sufficient duration.

Radioactive phosphorus is also useful in chronic myelogenous leukemia. It may be combined with radiation therapy or arsenic treatment if pressure symptoms are severe.

PHENYLHYDRAZINE

Phenylhydrazine, $C_6H_5.NH.NH_2HCl$, is employed against polycythemia vera because of its destructive action on red blood cells.

In polycythemia vera phenylhydrazine or acetyl phenylhydrazine, 0.1 Gm. daily, is administered by mouth in capsules until the hemoglobin falls below 100 per cent, a further decrease being expected after stopping the drugs. A total dose during any one period should not exceed 2.0 Gm.

The effect of phenylhydrazine is due largely to a widespread red cell hemolysis. Satisfactory response is obtained in about 50 per cent of the cases of polycythemia vera. It becomes manifest, after several days, with a rise of leukocytes to 50,000 or more, followed by a decline of hemoglobin and erythrocytes. Other symptoms gradually disappear. There may be some bone marrow depression. Liver damage may follow the use of this drug. Treatment with phenylhydrazine is more dangerous than x-ray irradiation.

URETHANE

Urethane (ethyl carbamate) has recently been used in the treatment of leukemia. One to four grams of urethane are given orally. There is a fall in total white count, diminution in size of the spleen and enlarged lymph nodes, and a rise in hemoglobin. Its use may be attended by a slight toxicity including drowsiness and gastrointestinal upset. The therapeutic action may be associated with its inhibitory effect on mitosis which has been demonstrated with plant and animal cells.

Creskoff (1948) and his co-workers found urethane of definite but limited value in the treatment of chronic leukemia. Chronic myelogenous leukemia appeared more responsive than the lymphatic variety. These investigators used an average daily dose of 4 Gm. orally or intravenously.

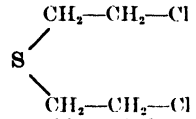
ARSENIC

The ability of inorganic arsenic to lower the leukocyte count in chronic myeloid leukemia has been known for years. Arsenic is claimed to be as effective as x-ray, but its use is not common where the latter is available. Furthermore, it is less desirable as all white cells may be killed, while x-ray tends to kill only the young cells in the marrow.

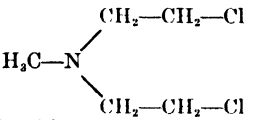
Arsenic may be administered as a solution of potassium arsenite, 0.2 cc. three times a day, after meals in fruit juice. Increase this dose by 1 drop a day until 0.6 cc. to 0.8 cc., three times a day, are given. When the white count is normal, administer a maintenance dose equal to the initial dose, by decreasing the dose 1 drop a day. Continue treatment indefinitely.

NITROGEN MUSTARDS

There has been considerable interest recently in the nitrogen mustards, which are relatives of mustard gas, in the treatment of leukemias.



Bis (β-chloroethyl) Sulfide (Mustard)



Methyl-bis (β-chloroethyl) Amine (A Nitrogen Mustard)

The compound most thoroughly studied is methyl-*bis* (β-chloroethyl) amine hydrochloride, which is given in a dose of 0.1 mg. per kg. body weight daily, or on alternate days for three to six doses. The single dose should not exceed 8 mg. The compound is given intravenously after it is dissolved in physiological salt solution.

Toxic effects of nitrogen mustards include nausea and vomiting, moderate lymphopenia, neutropenia, thrombocytopenia, anemia, and occasionally bleeding. Severe tissue damage may occur from leakage at injection site.

References

General

A Symposium on the Blood and Blood-forming Organs, Madison, 1939, University of Wisconsin Press.

Abt, H. L.: The Treatment of Leukemia, M. Clin. North America **28**: 187, 1944.

Forkner, C. E.: Leukemia and Allied Disorders, New York, 1938, The Macmillan Co.

Pxaegel, B. L., and Ross, J. F.: The Diagnosis and Treatment of Anemia, M. Clin. North America **30**: 1042, 1946.

Iron and Iron Compounds

Heath, C. W.: Iron in Nutrition—Requirements for Iron, J. A. M. A. **120**: 366, 1942.

Henderson, V. E., and Lucas, G. H.: On the Absorption of Iron, Am. J. Digest. Dis. **11**: 244, 1944.

Liver and Stomach Preparations

Castel, W. B.: Observations on the Etiologic Relationship of Achylia to Pernicious Anemia, Am. J. M. Sc. **178**: 748, 1929.

McSorley, J. G., and Davidson, L. S. P.: Sensitivity to Liver Extract, Brit. M. J. **1**: 714, 1944.

Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by Special Diet, J. A. M. A. **87**: 480, 1926.

Schwartz, S. O.: Pernicious Anemia, M. Clin. North America **28**: 214, 1944.

Subbarow, Y., Hastings, A. B., and Elkin, M.: Chemistry of Antipernicious Anemia Substances of Liver, Vitamins and Hormones, **3**: 237, 1945.

Folic (Pteroylglutamic) Acid

Bernheim, F.: The Interaction of Drugs and Cell Catalysts, Minneapolis, 1946, Burgess Publishing Co.

Clark, A. J.: General Pharmacology—Supplement IV to Heffter's Handbuch der experimentellen Pharmakologie, Berlin, 1937, Springer.

Hurst, H.: Biophysical Factors in Drug Action, Brit. M. Bull. 3: 132, 1945.

Wooley, D. W.: Recent Advances in the Study of Biological Competition Between Structurally Related Compounds, Physiol. Rev. 27: 308, 1947.

Anticoagulants

Allen, E. V., Barker, R. W., and Waugh, J. M.: A Preparation From Spoiled Sweet Clover, J. A. M. A. 120: 1009, 1942.

Allen, J. G., and Jacobson, L. O.: Hyperheparinemia: Cause of the Hemorrhagic Syndrome Associated With Total Body Exposure to Ionizing Radiation, Science 105: 388, 1947.

Butsch, W. L., and Stewart, J. D.: Clinical Experiences With Dicoumarin, J. A. M. A. 120: 1025, 1942.

Evans, J. A., and Boller, R. J.: The Subcutaneous Use of Heparin in Anticoagulation Therapy, J. A. M. A. 131: 789, 1946.

Jorpes, J. E.: Heparin: Its Chemistry, Physiology and Application in Medicine, London, 1939, Oxford University Press.

Jorpes, J. E.: Heparin in the Treatment of Thrombosis, New York, 1947, Oxford Press.

Link, K. P.: The Anticoagulant 3, 3-methylenebis (4-hydroxycoumarin), Federation Proc. 4: 176, 1945.

Peters, H. R., Guyther, J. R., and Brambel, C. E.: Dicumarol in Acute Coronary Thrombosis, J. A. M. A. 130: 398, 1946.

Coagulants

Davison, F. R.: Tissue Extracts and Blood Coagulation, Am. J. Physiol. 118: April, 1927.

Eagle, H.: Recent Advances in Blood Coagulation Problems, Medicine 16: 95, 1937.

Holoubek, J. E., Hendrick, J. V., and Hollis, W. J.: Toluidine Blue in Bleeding Associated With Thrombopenia, J. A. M. A. 139: 214, 1949.

Howell, W. H.: Theories of Blood Coagulation, Physiol. Rev. 15: 435, 1935.

Potter, E. L.: The Effect on Infant Mortality of Vitamin K Administered During Labor, Am. J. Obst. & Gynec. 50: 235, 1945.

Richards, R. K., and Shapiro, S.: Experimental and Clinical Studies on the Action of High Doses of Hykinone and Other Menadione Derivatives, J. Pharmacol. & Exper. Therap. 84: 93, 1945.

Radioactive Phosphorus

Editorial: Radioactive Phosphorus as a Therapeutic Agent, Ann. Int. Med. 25: 742, 1946.

Erf, L. A.: Radiophosphorus as the Treatment of Choice in Primary Polycythemia, Am. J. M. Sc. 1: 363, 1946.

Reinhard, E. H., Moore, C. V., Bierbaum, O. S., and Moore, S.: Radioactive Phosphorus as a Therapeutic Agent; A Review of the Literature and Analysis of the Results of Treatment of 155 Patients With Various Blood Dyscrasias, Lymphomas and Other Neoplastic Diseases, J. Lab. & Clin. Med. 31: 107, 1946.

Warren, S.: The Therapeutic Use of Radioactive Phosphorus, Am. J. M. Sc. 209: 701, 1945.

Warren, S.: Availability of Radioactive Isotopes—Announcement From Headquarters, Manhattan Project, Washington, D. C., Science **103**: 697, 1946.

Nitrogen Mustards

Goodman, L. S., Wintrobe, M. W., Dameshek, W., Goodman, M. J., Gilman, A., and McLennan, M. T.: Nitrogen Mustard Therapy —Use of Methyl-bis (beta-chloroethyl) Amine Hydrochloride and Tris (beta-chloroethyl) Amine Hydrochloride for Hodgkin's Disease, Lymphosarcoma, Leukemia and Certain Allied and Miscellaneous Disorders, J. A. M. A. **132**: 126, 1946.

Jacobson, L. O., Spurr, C. L., Guzman-Barron, E. S., Smith, T., Lushbaugh, C., and Dick, G. F.: Nitrogen Mustard Therapy; Studies on the Effect of Methyl-bis (beta-chloroethyl) Amine Hydrochloride on Neoplastic Diseases and Allied Disorders of the Hemopoietic System, J. A. M. A. **132**: 263, 1946.

Rhoads, C. P.: Nitrogen Mustards in the Treatment of Neoplastic Disease, J. A. M. A. **131**: 656, 1946.

Urethane

Creskoff, A. J., Fitz-Hugh, T., Jr., and Frost, J. W.: Urethane Therapy in Leukemia, Blood **3**: 823-966, 1948.

Hirschboeck, John S., et al.: Effects of Urethane in the Treatment of Leukemia and Metastatic Malignant Tumors, J. A. M. A. **136**: 90, Jan. 10, 1948.

Paterson, E., Haddow, A., Thomas, I. A., and Watkinson, J. M.: Leukaemia Treated With Urethane Compared With Deep X-Ray Therapy, Lancet **1**: 677-682 (May 11), 1946.

CHAPTER XXII

BIOLOGICALS

V. HORMONES

"Physiology has revealed the presence in the animal body of organs constantly making and adding to the blood substances rivaling the most potent of alkaloids in the intensity of their action, in modifying, stimulating, depressing, or regulating the activity and metabolism of the body and its organs.

"Already preparations of these hormones, the natural drugs of the body, play a large part in the treatment of disease and normal development. . . . No branch of modern therapeutics can show triumphs more genuine or more dramatic."—Sir Henry H. Dale, M.D., F.R.S.

Endocrinology has made rapid strides the past decade in laboratory and experimental knowledge; there has, however, been a slower application of these findings in the field of practical medicine. The most significant recent contributions have perhaps been in the field of antithyroid drugs, radioactive iodine in the treatment of toxic goiter, and those dealing with the relations of estrogens and androgens to carcinoma of the breast and prostate, respectively.

Definition of Hormones.—Hormone, a name derived from the Greek word meaning to excite or arouse, may be defined as a *chemical substance produced in an organ, which being carried to another organ or tissue by the blood stream influences its activity.*

Chemistry of Hormones.—Developments in the chemistry of the hormones have been so great in the past few years that it is almost impossible to give a complete résumé of their present position. New developments appear so rapidly that anything written today may need revision tomorrow. The accompanying diagram (Fig. 34) shows the general relationship of the hormones. It is shown that the control of the endocrine glands appears to be closely associated with the anterior lobe of the pituitary body.

The hormones show a wide diversity in their chemical structure. Thus thyroxin is an iodine derivative of an amino acid, tyrosine; testosterone is a sterol; insulin is a polypeptid. These substances are active in extremely small dilutions and exist in the blood and in the glands in small quantities. One-tenth of a milligram of insulin produces hypoglycemia in a two-kilogram rabbit, while epinephrine extracts exert demonstrable effects in dilutions greater than one in twenty million.

Another interesting fact is that each hormone is apparently identical regardless of the source. Thus insulin derived from beef pancreas is apparently identical with that elaborated by the human body. Consequently, the hormones, unlike other tissue proteins, give no anaphylactic reactions when pure preparations are injected.

Physiology of Hormones.—The glands of internal secretion may be considered a series of remote control organs concerned with the communication of impulses and the correlation of processes. They may be considered as *catalytic agents.* A catalyst does not initiate processes, but is able to increase markedly the rate of a chemical reaction already

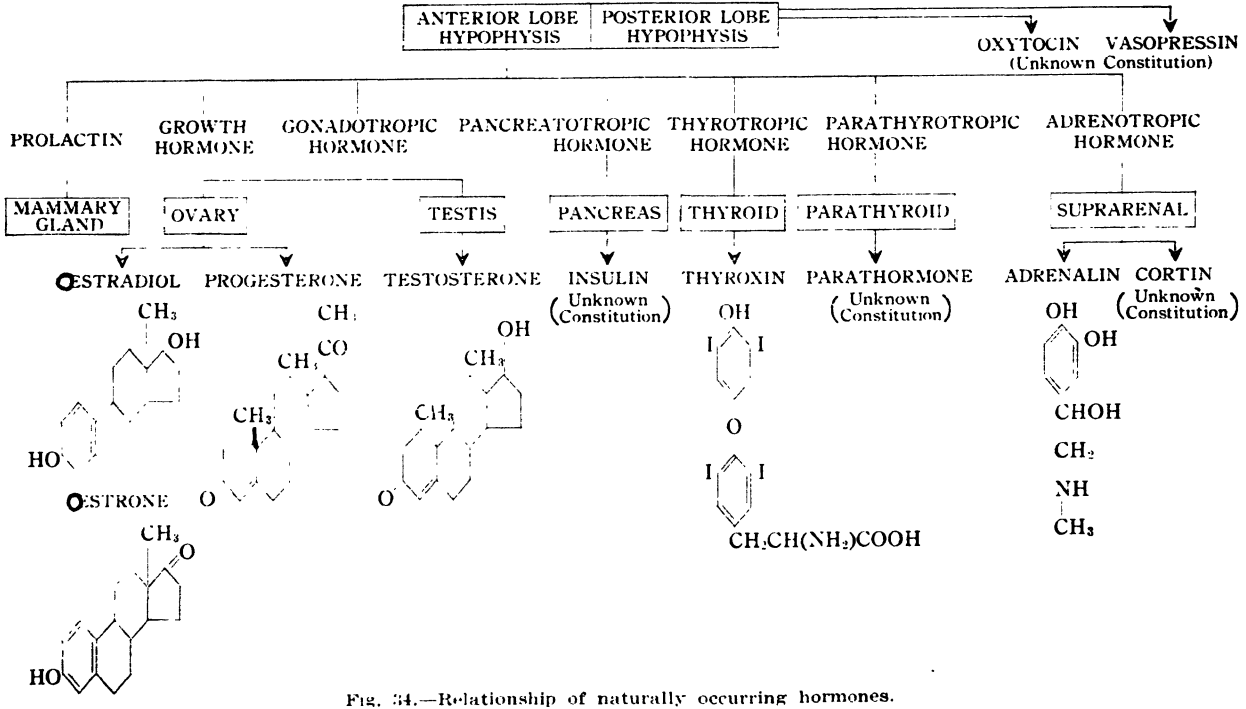


Fig. 34.—Relationship of naturally occurring hormones.

under way. It is known that a depancreatized body can use dextrose, but with the aid of insulin, the rate of sugar metabolism is greatly increased. Furthermore, the body can use oxygen without thyroid secretion, but in the presence of a normal supply of the hormone the rate of using oxygen is increased 60 to 70 per cent.

More recently, drugs having an antagonistic action toward the endocrine glands have been under observation. Thiourea and related compounds interfere with the thyroid hormone and depress basal metabolism in normal and hyperthyroid individuals. Alloxan has a selective toxic action on the beta cells of the islet tissues of the pancreas causing diabetes mellitus. Certain drugs are believed to stimulate the formation of endocrine substances. Recent evidence suggests that the antidiuretic effect of a number of drugs may be due to the production of an increased output of the antidiuretic hormone of the neutral lobes of the pituitary gland.

Endocrine Therapy.—In applying organotherapy, the patient and the preparation must be carefully studied and understood. The individual characteristics of the patient and the contents of each preparation must be known.

Rarely is each case a simple deficiency of a certain gland; in most patients there is present a deficiency or dysfunction of several glands which makes the task a more difficult one. In some instances there is a tendency to use pluraglandular therapy in the hope of correcting the deficiency. *Never use simultaneously even two endocrine preparations which have an opposite action on the organism.*

Factors Limiting Glandular Therapy.—Several factors may account for some of the lack of ability to correct glandular dysfunction by substitution therapy. The most common are: (1) difficulty in supplying hormones according to the needs of the body, (2) lack of ability of endocrine products to replace the normal endocrine secretions, (3) variability of body response to hormones administered, (4) lack of response following continued administration of glandular extracts, and (5) lack of knowledge concerning the interrelationships between the vitamins and hormones. It is known that vitamins may inhibit the action of hormones, and it has also been conclusively demonstrated that certain vitamin deficiencies are directly correlated with glandular deficiencies.

Hormone Assays are essential for correct diagnosis and for checks on therapy. Laboratory facilities should be available for determining the production of various hormones and for estimating concentrations in blood and urine. Apparatus for the determination of basal metabolism is most essential. It is necessary to be able to make simple chemical tests, including determinations of sugar, sodium, potassium, calcium, phosphorus, phosphatase, total protein, albumin, globulin, uric acid, creatinine, etc. Roentgen examination and endometrial biopsies are other means of securing important information.

Interrelationships of Hormones.—It is a common error to regard the hormones as agents involved in some specific reaction in the body. Such views are entirely inadequate to account for their great influence on the body. In fact, no single hormone or endocrine gland acts wholly by itself, and it is impossible to affect the activity of one without modifying the activity of the others. Although the exact mode of interaction has not been determined, there are, it appears, three possible ways in which one endocrine gland may influence another. These are:

1. *The secretions of two endocrine glands may exert opposite effects upon the same organ or tissue;* for example, insulin increases the

quantity of carbohydrate stored in the muscle as glycogen, while epinephrine causes a decrease.

2. *Dysfunction in one gland may alter the function of other endocrine glands;* for example, castration in childhood is followed by excessive growth in the long bones. This abnormal growth may be due to the liberation of the growth-promoting activity of the anterior pituitary from the inhibitory influence of the gonads that normally become active at puberty. Another example: the pituitary produces a substance which stimulates the growth and activity of the adrenal cortex, and if the pituitary is destroyed, the cortex atrophies, hence the adrenal depends on pituitary secretion for its ability to produce cortical hormone.

3. *The involvement of two or more endocrine glands may result in a complexity of symptoms;* for example, pancreatic diabetes and thyroid dysfunction might occur in the same individual.

These three typical examples show how closely related the endocrine glands are. The interrelationship seems centered about the anterior pituitary gland; for example, the pituitary, often called the master gland, controls the gonads and has an important function over the thyroid, pancreas, adrenals, and probably the parathyroids. The adrenal medulla, adrenal cortex, pancreatic islands and pituitary all influence carbohydrate metabolism, and the pituitary, adrenal cortex, thyroid, and gonads play an important role in the development and maintenance of sexual activity. In consequence, it is not difficult to imagine how dysfunction of the pituitary may produce complex disturbances in bodily function.

Endocrine Preparations.—The advent of the chemically pure hormones and the physiologically active synthetic hormone preparations have produced many advances in endocrine therapy.

The basic principle of endocrine therapy is to correct a deficiency state of the endocrine system. It may be assumed that each endocrine gland secretes one or more specific hormones which are given to the blood or lymph and influence in some manner the activity of the body. They exercise supervision over growth, nutrition, and sex, and influence mentality and personality. They are closely related and may have stimulating and inhibitory action on each other. Thus, the sex hormones have been administered in extremely large doses to depress anterior pituitary activity.

A new phase in endocrine therapy was marked by the appearance of synthetic chemical substances of a chemical constitution unrelated to the natural hormones but possessing similar physiological activity. The first of these, AT.10, dihydrotachysterol, when administered orally, has been successfully used to raise blood calcium in thyroid tetany. Another synthetic compound, diethylstilbestrol, chemically unrelated to the natural estrogens, possesses estrogenic activity following oral or parenteral administration.

The ever increasing number of endocrine preparations makes it almost impossible for a busy practitioner or student to evaluate their efficiency properly. The author will try to present that material most useful to the average practitioner. The consensus on endocrine therapy will be presented. Representative endocrine preparations will be given. Omission of any product must not be construed as an expression of opinion against it.

The glands which we are especially concerned with are the pituitary, thyroid, parathyroid, pancreas, and the sex glands; of these the thyroid, parathyroids and pancreatic islands apparently secrete but one hormone each, the adrenals and gonads at least two each, and the pituitary eight

or more. Little is known concerning the functional importance of the thymus and pineal glands. The following glands will be discussed:

Pituitary	Adrenals
Thyroid	Sex Hormones
Parathyroid	Pineal
Pancreas	Thymus

PITUITARY

The pituitary (hypophysis) is a small gland lying in the sella turcica at the base of the brain. It is composed of two main lobes, the anterior (glandular) portion and the posterior (nervous). The whole structure may be removed or destroyed without producing death. It does, however, play an important role in bodily welfare. The anterior and posterior lobes have entirely different histological structures and will be discussed separately. The posterior lobe secretes two demonstrable hormones, while the anterior lobe secretes eight or more active principles.

Little is known of the significance of the pars intermedia except that its extracts cause expansion of melanophores in amphibia and fish. This portion of the gland which is derived from the posterior walls of Rathke's pouch and is in intimate contact with the posterior lobe is glandular in structure and is said to secrete a substance which Zondek calls intermedin. It is not available clinically, but there is some evidence that it is of use in the treatment of diabetes insipidus. It is said to differ from pitressin in that it checks only water output, while pitressin reduces both water and sodium chloride excretion (Zondek and Krohn, 1932).

POSTERIOR PITUITARY

Extracts of the posterior lobe of the pituitary produce a marked effect on plain muscle, especially that of blood vessels and the uterus. The parenteral administration of such extracts is usually followed by an increase in blood pressure which is maintained over a long period of time. Repeated administration may have diminished pressor effect if repeated too soon after the initial injection. The increase in blood pressure is due to the constrictive action of the drug on the smooth muscle of the vessels. The action is not consistent in all individuals, some show slight response and others even show a lowering of blood pressure. The heart is thought to be depressed by vagus response to a high blood pressure or by direct depressant action on the myocardium because of coronary vessel constriction. Pituitary extract increases the tone of the intestinal tract, and is also thought to delay absorption of moisture from this organ. This latter action may account for its antidiuretic action. The bladder musculature is stimulated, especially if in an atonic state. Posterior pituitary extract may accelerate the output of milk but does not necessarily increase the amount of milk. Of great therapeutic importance is the oxytocic action of pituitary extract; it stimulates the uterus to contract by direct muscle action. This action is especially evident in pregnant animals.

The posterior lobe of the pituitary provides a pressor and an oxytocic substance. Any destructive lesions involving the integrity of the nervous connection from the supra-optic nuclei through the infundibulum or involving the posterior lobe result in polyuria. The physiological significance of the pressor material is unknown. Physiologic oxytocic activity is thought to be present during labor, but this has not been confirmed experimentally.

In 1928, Kamm and others were able to separate two active principles from the posterior lobe. One, which they called *alpha-hypophamine*

(also called pitocin), causes contraction of the uterus and smooth muscle. The other, which they called *beta-hypophamine* (also called pitressin), raises blood pressure and has a diuretic-antidiuretic action. Permanent polyuria results from destructive lesions involving the posterior lobe.

Therapeutic Uses.—Hypofunction of the posterior lobe produces the clinical entity of diabetes insipidus. No accepted clinical syndrome is associated with hyperfunction of the posterior lobe.

Diabetes Insipidus is characterized clinically by polyuria, excessive thirst, and pathological lesions in the region of the supra-optico-hypophyseal tracts. The lesions probably interfere with the formation of the secretion of the posterior pituitary. *Treatment:* Preparations of posterior pituitary are helpful. Solutions of posterior pituitary may be injected subcutaneously, sprayed in the nose, in doses of 1 cc. as needed, usually once daily. The powder of posterior pituitary (40 to 50 mg.) may be snuffed in the nose daily. *Pitressin tannate* in oil may be injected intramuscularly in doses of 0.5 to 1 cc. The active constituent is slowly liberated and one injection may be effective over a period of forty-eight hours.

Extracts of posterior pituitary are employed to increase the force of uterine contraction in labor and to prevent postpartum hemorrhage. See Chapter XVI on Oxytocics.

Posterior pituitary extracts are also useful in preventing hemorrhages in certain operations such as tonsillectomies and prostatic resections. Areas that exhibit an oozing bleeding may be quickly wiped with a solution of posterior pituitary; the styptic action usually makes the operative field suitable for surgery.

Posterior pituitary has been used for stimulating bowel musculature in the treatment of postoperative paralytic ileus and bowel distention.

Standardization.—An International Standard preparation of posterior pituitary contains 1 unit of activity in 0.5 mg. The Official U.S.P. method measures only oxytocic activity. The assay is based on the production of contractions in the excised uterus of the virgin guinea pig.

Toxicology.—Absorption of excessive amounts of posterior pituitary may cause gastrointestinal cramps and evacuation. The use of posterior pituitary is contraindicated in heart disease because of its coronary constrictive action. The addition of epinephrine or ephedrine may antagonize the effect of pituitary on the coronary vessels and it also prolongs the pressor effect of posterior pituitary. In pregnancy the drug might empty the uterus. Large doses of posterior pituitary may favor gastric ulcer formation due to its local vasoconstriction action.

ANTERIOR PITUITARY

The anterior lobe of the pituitary is the "master gland" of the endocrine system, the secretions of which are essential for the physical and mental well-being of the individual. Our knowledge of its function has resulted from the experimental work of such investigators as Evans, Riddle, Zondek and others, and has followed in the wake of surgeons, such as Cushing and Homans.

At least a dozen or more types of physiological effects have been attributed to the anterior lobe. Nine or more of these have been attributed to distinct and separate hormones, namely, (1) a growth hormone concerned with the development of the body; (2) a hormone which stimulates the growth and maturation of the ovarian follicles, which in turn brings on changes characteristic of estrus; (3) a hormone which causes luteinization of the ovarian follicles; (4) a hormone which is essential

for normal thyroid development; (5) a hormone, named prolactin, which produces lactation in mammals, and possibly plays a part in mammary gland proliferation; (6) a diabetogenic hormone which decreases the hypoglycemic response to insulin and the absence of which leads to hypoglycemia; and (7) a ketogenic hormone, which increases the ketone content of the blood in rabbits and rats. In addition to these hormones, the existence of other principles has been demonstrated; among these are (8) the adrenotropic hormone which stimulates the adrenal cortex and, (9) the thyrotropic hormone which stimulates the thyroid.

More recently, Evans of the University of California has isolated an adrenocorticotropic hormone and also a purified growth hormone. Preliminary reports on the effects of the former are contradictory and further observations will be necessary to determine the status of this material.

It has been shown that in patients showing a loss of pituitary function, as in Simmond's disease and chromophobe adenoma, there is an evidence of hypothyroidism, hypofunction of the adrenal cortex, and hypogonadism. Patients with hypopituitarism sometimes show typical Addison's crises which have to be treated with injections of adrenal cortex extract and sodium chloride and dextrose. These patients do not appear to become pigmented as frequently as do patients with Addison's disease caused by destruction of the adrenal glands.

Anterior Pituitary Extracts.—Despite the labor and care expended in separating various principles of the anterior pituitary, none of the hormones is available in pure form.

Evans' purified growth hormone is probably as pure a form of this substance as has yet been obtained from the anterior pituitary. This new preparation is of great interest but has not been tried adequately in man. Preparations of growth hormone available up to the present time have proved of little value clinically.

Preparations of thyrotropic hormone will cause temporary increase in basal metabolism in many patients in whom some functional thyroid tissue is present. The metabolism always returns to its initial level or even lower with prolonged administration.

Conditions Resulting From Dysfunction of Anterior Pituitary

Certain diseases are associated with hyperactivity and hypoactivity of the anterior pituitary. Because of the multiplicity of the physiological effects of the gland, these abnormalities take various forms. Theoretically, in diseases due to deficiency of the anterior pituitary substitution therapy would be indicated. This is at present impractical because pure extracts are not available. On the other hand, treatment of hyperactivity is difficult, as surgery is difficult and roentgen irradiation is often ineffective. Depression by use of drugs is of limited value and often little understood. The following are common pituitary disorders:

Anterior lobe	Hyperactivity	Acromegaly Gigantism Pituitary basophilism (Cushing's syndrome)
	Hypoactivity	Dwarfism Pituitary cachexia (Simmonds' disease)
Posterior lobe deficiency or hypothalamic lesion		Diabetes insipidus
Anterior and posterior lobe deficiency or hypothalamic lesion		Dystrophia-adiposogenitalis (Fröhlich's syndrome)

GIGANTISM AND ACROMEGALY.—Eosinophilic tumors of the anterior lobe of the pituitary are often associated with excessive production of the growth hormone. *Gigantism* usually results if the stimulation occurs before closure of the epiphysis, and *acromegaly* occurs after union of the epiphyses.

Treatment.—Radiation therapy may be effective, but other functions of the anterior pituitary may of course be affected. Give 300 r. daily for nine days, through three different portals, and repeat once in two months.

Administration of male or female sex hormones, or thyroid, has been suggested as means of depressing the hyperactive pituitary, or for closing the epiphyses and stopping further growth. In gigantism use of testosterone should be tried because growth in height is usually stopped with no side effects of any consequence.

Surgery should be resorted to if other measures fail.

CUSHING'S SYNDROME (PITUITARY BASOPHILISM).—This condition was first described by Cushing in 1932, and he attributed it to the presence of a basophilic adenoma of the pituitary. The condition is now considered by some investigators to be secondary to primary adrenal disease. The condition is characterized by a plethoric type of obesity of the trunk, face, and buttocks. The fatty deposits may be tender and painful. Other characteristics are purplish striae over the abdomen, hirsuitism, hypertension, diabetes, and lowered sexual activity. It is mainly a disease of adult women, but a few cases have been reported in men.

Treatment.—Treatment of this condition is unsatisfactory. Some patients exhibit a condition intermediate between Cushing's disease and the adrenogenital syndrome. Testosterone propinate, 25 mg. intramuscularly daily, is recommended by some clinicians. This agent is thought to increase the formation of tissue from protein and thus to counteract the excessive glycogenesis. Those not improved by this treatment may respond to roentgen irradiation.

DWARFISM.—Hypophyseal dwarfism, due to lack of development or destructive lesions of the pituitary, may occur if the decreased action of the gland occurs during the growth period. These dwarfs are well proportioned but show a sexual infantilism. Since the epiphyses remain open, slow growth may occur. They are, as a rule, normal mentally.

In contrast to the *pituitary dwarf* just described there is the *genetic dwarf* who is normal in all respects except in size.

Treatment.—Anterior pituitary "growth preparations" have been tried with little success.

Female dwarfs may be aided by administration of chronic gonadotropin and estrogens. *Dosage:* Chorionic gonadotropin—500 units two or three times a week subcutaneously. Diethylstilbestrol—0.25 mg. daily, by mouth. Thyroid, in doses of 30 to 60 mg. daily, orally, may be of value.

Male dwarfs at ten years of age may be aided by chorionic gonadotropin and testosterone, to induce puberty. This will be of benefit only until closure of the epiphyses and will not increase growth. *Dosage:* Chorionic gonadotropin—500 units two or three times a week, subcutaneously. Testosterone propinate—10 to 25 mg. intramuscularly, twice weekly.

PITUITARY CACHEXIA (SIMMONDS' DISEASE).—This is a rare disease associated with atrophy of the anterior lobe of the pituitary, occurring in adult life. The main features of this disease are progressive emaciation, asthenia, and cachexia. The skin becomes wrinkled and dry. The metabolism of the body is reduced. Patients become apathetic, ex-

hausted, and senile. It may occur at any age; it may run a rapid course with death in a few months, or a chronic course, extending over several years.

Treatment is difficult. The administration of anterior pituitary extracts are of little value. The use of desoxycorticosterone or adrenal cortex extract, sodium chloride, thyroid, and testosterone propinate have been reported of value in the treatment of secondary insufficiencies.

A high caloric, high vitamin diet plus general supportive measures are indicated for this disease.

DYSTROPHIA ADIPOSOGENITALIS (FRÖHLICH'S SYNDROME).—This condition may be due to dysfunction of the pituitary gland but its chief symptoms are now looked upon as a result of pressure on the hypothalamus and its adjacent structures. The picture lacks the cachexia of Simmonds' disease and possesses the obesity and sexual infantilism associated with dwarfism. The chief symptoms are obesity, faulty skeletal development, and genital hypoplasia. The obesity is often the female type characterized by deposition of fat over the mammae, hips, upper parts of the thighs, and lower abdomen. The reproductive organs are underdeveloped. The hands are plump with tapering fingers. In males the voice remains effeminate. When the disorder is due to a neoplasm, symptoms such as headache, somnolence, lassitude, and vision changes are prominent.

Treatment.—Simple reduction of diet to control obesity may be sufficient in this condition. X-ray therapy may be indicated if there is evidence of brain tumor. Sexual development may be hastened by the use of gonadotropic pituitary extracts.

PREPARATIONS

Pure extracts of anterior pituitary hormones are not available. The N.F. contains a whole pituitary and an anterior pituitary preparation. There is little indication for their clinical use.

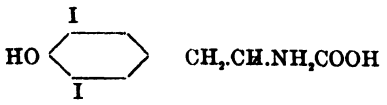
THYROID GLAND

The thyroid gland, one of the most important of all endocrine glands, consists of two lobes connected by the isthmus. The individual lobes are located on each side of the larynx, while the isthmus crosses the midline between the two lateral structures.

Three important developments are of particular interest: (1) the use of antithyroid drug, (2) the use of radioactive iodine, and (3) the irradiation of the pituitary.

The administration of thyroid preparations in the treatment of certain diseases is one of the most satisfactory examples of organotherapy. The first important step in the elucidation of the chemistry of the thyroid gland was the discovery of iodine in the gland by Bauman (1895). He was the first to prepare a nonprotein extract of thyroid which contained the iodine and was physiologically active. In 1915 Kendall isolated the amino acid, *thyroxin,* which contained 65 per cent of iodine and was proved to be the active principle of the hormone. Harington (1926) prepared large amounts of this substance and established its constitution. The final proof of the structure was furnished by Barger and Harington (1927) who synthesized thyroxin by coupling two molecules of diiodotyrosine.

Three organic iodine compounds are present in thyroid tissue; diiodotyrosine, thyroxin, and thyroglobulin. Harington (1935) believes that the hormone is produced in the following manner; inorganic iodine acts



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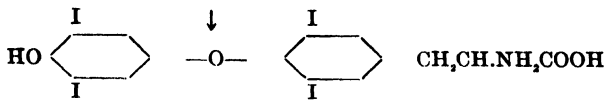


Thyroxin ($C_{15}H_{11}O_4NI_4$)

on tyrosine to give diiodotyrosine, two molecules of diiodotyrosine unite to form a molecule of thyroxin. Thyroxin and diiodotyrosine are then linked through an amino acid to form iodothyroglobulin. Iodothyroglobulin probably serves as the form in which the hormone is stored in the gland and is converted to a simple polypeptid which is released from the gland into the blood stream.

Thyroxin apparently may be formed by other tissues than the thyroid. Studies with radioactive iodine have shown that thyroxin may be formed in completely thyroidectomized animals.

Function.—Thyroxin has a very remarkable effect on the metabolic activity of the body. If it is formed in appropriate amounts normal development takes place. If it is deficient, as in young animals after thyroidectomy, the following changes occur: the skin becomes dry and thickened and the hair falls out; the generative organs fail to grow; there is retardation of skeletal growth; dullness and apathy are very pronounced. Excessive thyroid feeding produces the following results: loss of body weight, disappearance of the fat deposits, gastroenteritis, nervousness, and tachycardia.

The thyroid gland is intimately related to other endocrine glands. Removal of the thyroid gland produces an enlargement of the pituitary gland, while pituitary enlargement occurs with myxedema. It has been shown that removal of the hypophysis (anterior pituitary) produces a condition identical with myxedema, and hyperplasia of the thyroid can be produced by administration of anterior pituitary extracts. The thyroid hormone influences many phases of metabolism. The consumption of oxygen is increased by its action. Heat production is correspondingly increased. These phenomena are the basis for a test for increased or decreased functional activity of the thyroid—the basal metabolism test.

The utilization of sugar is increased by thyroxin; glycogen stores are sharply reduced, and the ability of the liver to store glycogen is diminished. Water retention and excretion appear to be linked with thyroid activity. The thyroid gland enlarges during menstruation, pregnancy, puberty, and menopause. Mental activity and neuromuscular activity are influenced to a great extent by thyroxin. Myxedematous patients are dull and lethargic while in hyperthyroidism the opposite effect is apparent. Proper thyroid function is necessary for normal involution of the thymus. Hyperthyroidism leads to increased calcium excretion and parathyroid hypertrophy. The gonads are affected by the thyroid gland and carbohydrate metabolism is also related to the thyroid secretion.

Iodized Proteins Simulate Thyroxin Activity.—Recent studies have thrown light on the ability of iodized proteins to simulate thyroxin activity. Therapeutic effects of iodized whole serum protein have been demonstrated in human beings with athyrosis. The therapeutic pattern

of stimulation by these artificially iodized proteins is probably the same as when desiccated thyroid is given, as shown by successful isolation of thyroxin from the hydrolysis products of iodized casein.

Mann and his coworkers (1942) gave us some indication of the pathway of synthesis of the thyroid hormone. They injected radioactive iodine into dogs, and the relative amounts of inorganic iodine, diiodotyrosine, and thyroxin in the thyroid substance were calculated from the relative specific radioactivity of these fractions. They concluded that diiodotyrosine seems to be the precursor of thyroxin. There seems to be a close chemical and functional relationship between the thyroid protein and the artificially iodized proteins. There is the possibility of preparing an active therapeutic agent in the laboratory on a large scale.

Conditions Resulting From Dysfunction.—The manifestations of thyroid dysfunction are exceedingly variable. Simple goiter, hypothyroidism (myxedema and cretinism), and hyperthyroidism are the usual thyroid disturbances.

Simple Goiter.—Simple, or colloid, goiter is due to thyroid hyperplasia resulting from lack of iodine. Cases occur most frequently in areas where drinking water is deficient in iodine. Swelling in the neck is the usual manifestation. If growth compensation is inadequate, hypothyroidism results.

Treatment.—Prophylactic treatment consists in supplying adequate iodine (0.1 mg. daily for man). The use of iodized salt in the salt shaker is usually sufficient.

Surgery may be necessary once a simple goiter is formed, especially if pressure symptoms are present. Children may respond to the administration of potassium iodide, 1.5 mg. weekly, but such treatment is probably contraindicated in older patients as it is ineffective and may even induce hyperthyroidism.

Hypothyroidism

Hypothyroidism may result from atrophy of the thyroid, from colloid goiter, or infection, or from surgical removal. Cretinism and myxedema are common clinical entities of hypothyroidism.

CRETINISM.—This condition may result from failure in the embryonic development of the thyroid or its atrophy during fetal life or early infancy. Two forms are described. The endemic form is due to goitrous degeneration of the gland. The failure of development of the gland in this form may be due to lack of iodine in the mother. The other form, the sporadic form, has the same underlying etiology as found in myxedema.

The most characteristic symptom of this condition is the complete cessation of physical and mental development, resulting in dwarfism and idiocy. Cretins are pot-bellied and ugly; the hair is thick and coarse and the skin dry and pale. The tongue is thick and protrudes through the gaping mouth. The hands and feet are spade-like and the lips are thick. As in myxedema of adults the basal metabolic rate is low. The use of blood cholesterol determination is an excellent accessory diagnostic test, since elevated cholesterol content is said to occur uniformly in hypothyroidism when untreated.

Treatment.—Administer thyroid in adequate amounts by mouth. Cretins require fairly large doses, from 0.06 to 0.2 Gm. daily if necessary. Treat other symptoms as they arise.

MYXEDEMA.—This condition results from atrophy of the thyroid glands. It is usually insidious in its development, with a gradual retardation in the physical and mental functions. Its deficiency causes

a marked reduction of the basal metabolic rate, a fall in body temperature, and a slower than normal pulse rate. The face and hands become puffy and swollen, due probably to the formation of a subcutaneous connective tissue. The skin becomes thick, and the hair tends to fall out. Sensitiveness to cold is a characteristic symptom. The swelling of the mucous membranes gives rise to a husky, bass voice; deafness may occur due to swelling of the tympanic membrane. Speech is slow due to difficulty in enunciation.

Treatment.—Administer 0.1 Gm. of thyroid daily in total myxedema. This will maintain the basal metabolic rate at about minus 5 per cent. It may be necessary to adjust this dosage to meet the requirements of the individual. Administer the corrected dosage indefinitely. Thyroid is preferred over thyroxin as the latter is expensive and irregularly absorbed. If intravenous therapy is indicated, use thyroxin in doses of 0.2 to 2 mg.

Hyperthyroidism

In this condition excessive thyroid hormone is produced, probably due to excessive activity of the anterior pituitary. The excess of hormone causes increased tissue oxidation and sympathetic nerve stimulation, associated with hunger, loss of weight, nervousness, and exophthalmus in younger persons.

Thyroidectomy, antithyroid drugs, and radioactive iodine are useful in this condition but do not attack the underlying cause. The two antithyroid drugs most often used are thiouracil and propylthiouracil. The latter is less toxic but is not free from toxic manifestations by any means. These drugs have been used to treat the disease and also to prepare the patient for operation.

The introduction of *antithyroid* drugs represent an important advance in preoperative preparation of patients with toxic goiter. It is possible to eliminate the thyrotoxicosis more completely than formerly with iodine. Propylthiouracil is of greatest value in preoperative preparation of patients who have thyrotoxicosis in severe form. The mortality is almost nil and hospitalization is shortened.

The percentage of cures appear to be related to the length of time that the basal metabolism is maintained at normal level before treatment is discontinued. Patients not cured by one course may respond to a second or third. Caution should be used in concluding that the treatment is effective, as spontaneous remissions of the disease are common. The development of these drugs represent an important advance in the treatment of toxic goiter but are not the final answer.

It is generally agreed that the antithyroid drugs are most valuable in the treatment of persistent recurrent symptoms following subtotal thyroidectomy, and the treatment of patients in whom surgery is contra indicated.

The use of *radioactive iodine* represents another approach to the problem of treating toxic goiter. When small amounts of radioactive iodine are administered, thyroid cells are destroyed, producing areas of fibrosis in the thyroid gland. Myxedema may be produced in the experimental animal. When administered to patients with toxic goiter in proper amounts, cures are effected in a large percentage of the cases. This new form of treatment is of great interest but more trials are necessary in order to determine the incidence of cures and the incidence of late complications, if any.

The question may arise in regard to the effect of radioactive iodine on carcinoma of the thyroid. Seidlen, et al. (1946), reported a beneficial action with hyperfunctionary metastases of adenocarcinoma

of the thyroid. Most carcinomatous cells, however, take up little radioactive iodine, and little effect is to be expected.

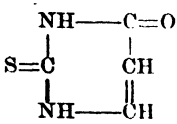
Treatment.—Best results follow subtotal thyroidectomy after preparation with iodine or thiouracil.

Thyroidectomy: If surgery is the treatment of choice, the patient is first treated with iodine or thiouracil to return him to a normal state suitable for the operation. For mild cases iodine is preferred, for severe cases thiouracil may be indicated.

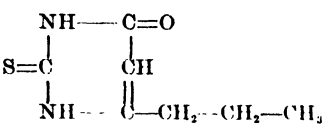
If *iodine* is used, administer potassium iodide solution or compound iodine solution, 0.3 cc. three times a day by mouth. After from 10 to 20 days, the basal metabolic rate will probably reach a reasonably stationary low level and the patient is ready for surgery. Continue iodine for one month after operation.

If *thiouracil* is selected, administer 0.2 Gm. three times a day until B.M.R. has fallen to about zero. Watch patients for signs of dermatitis. Make a blood count every other day. If a severe depression of white cells occurs, substitute iodine for thiouracil.

Thiouracil interferes with the formation or release of the thyroid hormone. When administered continuously for ten months or more, and then stopped, about 50 per cent of the patients do not experience a recurrence of the disease. Patients must be under careful supervision to detect granulocytopenia. *Dosage:* The initial dose of 0.6 Gm. daily is gradually diminished to 0.4 Gm. or 0.2 Gm. daily in order to maintain the B.M.R. at about zero per cent. Iodine therapy should not be given concurrently. If goiter is nodular, this treatment is definitely contraindicated as malignant degeneration of the nodules may occur.



Thiouracil



Propylthiouracil

Other Uses of Thyroid.—In addition to its use in replacement therapy in hypothyroid conditions, thyroid is used clinically in various other conditions with somewhat irregular results. Thyroid extract may be used in *amenorrhea* for its stimulating effect on ovaries. It may be of some value in some types of *obesity*. It should only be given under a physician's supervision since in some obese patients there exists a sensitivity to thyroid extract. It causes loss not only of fat, but also of protein, and may give rise to untoward symptoms, such as cardiac and nervous disturbances, glycosuria, and exhaustion.

Thyroid has given good results in some cases of rheumatoid arthritis, epilepsy, hemophilia, osteomalacia, rickets, and in various skin diseases, especially psoriasis and ichthyosis. It is not generally recommended in these conditions, and should be used only when definitely indicated.

Standardization.—Thyroid preparations are standardized by their iodine content. The U.S.P. requires that thyroid contains not less than 0.17 per cent and not more than 0.23 per cent of iodine in thyroid combination.

PREPARATIONS

Thyroid, *Thyroideum*, U.S.P. The thyroid glands of domesticated animals. Contains about 0.2 per cent of iodine. *Dosage:* 60 mg. (1 grain).

Thyroid Tablets, *Tabellae Thyroidei,* U.S.P. The usual sizes contain 15 mg., 30 mg., 60 mg., and 120 mg.

Thyroxin, *Thyroxinum,* U.S.P. The active principle obtained from the thyroid gland or prepared synthetically; it contains not less than 64 per cent of iodine. *Dosage:* 0.5 mg. (1/120 grain). Thyroxin should always be given in minimum effective doses, which should be determined for each patient. A small cretin requires from 0.2 to 0.4 mg. (1/300 to 1/150 grain) every day or two. A patient with high grade myxedema requires 1.5 to 2.0 mg. (1/40 to 1/30 grain) daily.

PARATHYROID GLANDS

The parathyroid glands, usually four in number, generally rest upon the posterior aspect of the thyroid. In 1925, Hanson and Collip, working independently, succeeded in preparing an active extract from these glands which would prevent or relieve tetany in parathyroidectomized animals. Although comparatively little is known concerning the chemistry of the parathyroid hormone, all evidence points to the fact that the hormone is a protein-like substance.

Function.—The parathyroids function in the metabolism of calcium and phosphorus. If one stops substitution therapy with parathyroid extract in a parathyroidectomized patient four cardinal changes occur. There is *first* an immediate decrease in phosphorus excreted in the urine; *second,* the serum phosphorus level rises; *third,* the serum calcium level falls; *finally,* with the fall in serum calcium there is eventually a decreased excretion of calcium in the urine. If parathyroid extract is administered to a normal person these same four metabolic functions are altered in the opposite direction, i.e., one obtains hyperphosphaturia, hypophosphatemia, hypercalcemia, and hypercalcinuria.

Mode of Action.—The exact mechanism of parathyroid control over calcium and phosphorus is unknown. The hormone may act by increasing mobilization of calcium from bone, or it may act by increasing the excretion of phosphate by the kidney thus indirectly causing a rise in blood calcium. Evidence is available to substantiate both views.

Conditions Resulting From Parathyroid Dysfunction.—Certain clinical conditions are identified with hypoparathyroid and hyperparathyroid conditions. The most common of these are:

HYPOPARATHYROIDISM.—Parathyroid insufficiency is a distressing condition which fortunately is rather uncommon. It occurs in two forms: (1) the so-called idiopathic hypoparathyroidism, and (2) postoperative parathyroid insufficiency. The former is rare; the latter follows operations on the thyroid gland in about 1.5 per cent of thyroidectomies. The symptoms of insufficiency may occur within several days following operations on the thyroid or may be delayed for several weeks after operation. Hypoparathyroidism leads to *tetany.*

The clinical picture of postoperative parathyroid insufficiency leading to *tetany* is readily recognized: early symptoms consist of stiffness in the muscles of the extremities and face with numbness and tingling in the fingers. Carpopedal spasms of the hands may develop. Chvostek, Trousseau, and Erb's signs are positive. The voice becomes hoarse, the breathing tends to be stertorous, and later convulsive seizures may occur. The blood calcium at this time is low. Intravenous injection of calcium will stop the tetany promptly. Laryngeal stridor, carpopedal spasm, paresthesias, accompanied by the finding of a low serum calcium

(below 8 mg. per 100 cc. of serum) are diagnostic of hypoparathyroidism. Cataracts are present in almost all cases of long-standing duration.

Treatment.—Parathyroid extracts are of limited value in the treatment of hypoparathyroidism, or tetany, because tolerance develops after a few weeks and the hypocalcemia is no longer affected.

Acute Tetany.—This condition may be well treated by immediate intravenous injection of 20 cc. of 5 per cent calcium chloride solution, or 10 cc. of 10 per cent calcium gluconate solution. Parathyroid injection, 25 units three times daily, intramuscularly is indicated and becomes effective after about fourteen hours, while the calcium acts immediately.

Chronic Tetany.—For prolonged treatment of hypoparathyroidism, or tetany, activated sterols are indicated. The most widely used compound is *dihydrotachysterol,* also known as A.T. 10, which is closely related chemically to calciferol (vitamin D_2). The use of both vitamin D and dihydrotachysterol provide a potent means of treating chronic tetany. Vitamin D is given to promote calcium absorption from the bowel, and dihydrotachysterol to promote excretion of phosphorus from the kidney.

For treatment, administer 5 cc. of dihydrotachysterol (5 mg. per cc.) orally the first day and 2.5 cc. the second day. After this, 0.25 to 1 cc. may be given daily as needed to keep the calcium level normal. Administer vitamin D, 200,000 to 400,000 units of vitamin D to 1 cc. of dihydrotachysterol. Control treatment by simple urinary test for calcium (Albright, J. A. M. A. 112: 2572, 1939).

HYPERPARATHYROIDISM.—This may result either from adenomas or hypertrophy of the parathyroids or from overdosage of its hormone. Enlargement of the parathyroids is observed in such conditions as *osteitis fibrosa cystica, osteoporosis, renal calcinosis, metastatic calcifications, rickets, osteomalacia, multiple myeloma, nephritis with hypocalcemia and phosphorus retention.* All of these conditions are characterized by loss of calcium phosphate from the bones, but only one—*osteitis fibrosa cystica*—is caused by overactivity of the parathyroids. The hypertrophy of the parathyroids in the other conditions may be considered as a compensatory reaction tending to overcome a condition resulting from other causes, i.e., dietary deficiencies in rickets and osteomalacia.

The symptoms of hyperparathyroidism may be divided into three groups: (1) those due to bone disease, i.e., decalcification, pain, fractures, etc., (2) those due to renal disease, i.e., formation of calculi, polyuria, polydipsia, etc., and (3) those due to hypercalcemia, i.e., weakness, cardiac irregularities, pains, nausea and vomiting, etc.

The symptoms which are associated with bone disease include generalized decalcification, cysts, giant-cell tumors, fractures, and epulides. Almost any skeletal manifestation—a spontaneous fracture, a pain in the back, tenderness in the shins—may be the first symptom of the disease.

Treatment.—Acute hyperparathyroidism due to overdosage of the gland extract is associated with loss of water and salts, and renal failure. Treat by replacing water and salts. A high phosphate diet probably would aid in excretion or deposition of the excess calcium. *Chronic* hyperparathyroidism is best treated by surgical removal of tumors and excess gland tissue.

Standardization.—The U.S.P. Unit of parathyroid activity is equivalent to one-hundreth of the amount required to raise the calcium content of 100 cc. of blood serum of normal dogs 1 mg. within sixteen to eighteen hours after administration.

PREPARATIONS

Parathyroid Injection, *Injectio Parathyroidei*, U.S.P. (Parathyroid Solution, Parathyroid Extract). A sterile solution, in water for injection, of the water-soluble principle or principles of the parathyroid glands, which have the property of relieving the symptoms of parathyroid tetany and of increasing the calcium content of the blood stream. *Dosage:* Intramuscular, 25 U.S.P. units. The usual size contains 100 U.S.P. units in 1 cc.

Other parathyroid preparations are listed in the N.N.R.

PANCREAS

The pancreas is a gland having, in general, two functions: (1) it secretes into the intestine a digestive juice containing the enzymes trypsin, lipase, and amylase; (2) it secretes into the blood insulin, which regulates carbohydrate metabolism.

In 1889, Mering and Minkowski showed that the removal of the pancreas in animals gave rise to symptoms identical with those of diabetes mellitus in man. As early as 1909, the word insulin had been proposed to designate the internal secretion of the islets of Langerhans. Many attempts were made to secure an extract of pancreas suitable for the therapeutic treatment of diabetes mellitus. Finally Banting, Best and Collip (1922) obtained a preparation from the islands of Langerhans which was well suited to clinical uses. Insulin was isolated in a crystalline form by Abel (1926). The suggested empirical formula is $C_{45}H_{69}O_{14}N_{11}S$.

Since its introduction insulin has undergone relatively little modification until Hagedorn and his associates (1936) showed that the blood-sugar lowering action of insulin was prolonged when it was combined with protamine. Scott and Fisher found that the addition of zinc salt to a protamine and insulin mixture further prolongs the activity.

Recently the use of various *insulins* have been perfected. One interesting observation made by Dixon, et al. (1946), of the Mayo Clinic, was that they noted that the total insulin requirement was unaffected by total pancreatectomy.

Function of Insulin.—Insulin, the internal secretion of the pancreas, is formed in the islet tissue of this organ and passes into the general circulation. Its presence is indispensable for the normal maintenance of metabolism in mammals. The importance of insulin is appreciated upon examination of the physiological disturbances in the body which occur in the absence of its secretion (diabetes mellitus). The following are characteristic symptoms:

1. Pronounced hyperglycemia and glycosuria.
2. Lowering of respiratory quotient indicating incomplete combination of glucose.
3. Depletion of the glycogen stores in liver, muscle, and other tissues.
4. Increase in glucose-nitrogen ratio in the urine, likely due to an increase in the conversion of protein into glucose.
5. Development of acidosis due to imperfect fat metabolism.

These symptoms are relieved by the injection of insulin, and a normal metabolism is established.

The following are the principal functions of insulin:

1. Acceleration of glucose oxidation in the tissues.

2. Increase in the rate of glycogen formation in the tissues. We cannot say definitely whether insulin has a direct influence on the formation of liver glycogen or whether it inhibits hepatic glycogenolysis which is caused by other hormones. The fall in blood sugar following insulin injection is probably due to increase in glucose oxidation and to the increase in rate of glycogen formation.

3. Inhibition of carbohydrate formation in the liver from noncarbohydrate sources. Glyconeogenesis is thought to be under the control of certain other endocrine factors.

4. Prevention of the formation of ketone bodies which are formed as a result of incomplete carbohydrate metabolism.

Mode of Action of Insulin.—It is probable that insulin acts as a catalyst to cellular metabolism. Since relatively small amounts are necessary (2.5 mg. of crystalline insulin per day for an adult suffering from severe diabetes), the catalytic nature of insulin action seems quite probable. The nature of the underlying disturbance in diabetes is unknown and the mechanism by which insulin produces its effects is still unsettled. The scope of this book will not permit discussion of the various theories presented to explain the action of insulin.

Carbohydrate Metabolism.—Carbohydrate metabolism is controlled by a well-balanced interaction of various endocrine principles. The changes in metabolism are controlled, on the one hand by insulin and, on the other hand, by those endocrine secretions (anterior pituitary, adrenal cortex and thyroid) which are apparently antagonistic to the physiological action of the pancreatic hormone. The exact manner of these complex actions is unknown. They may be mediators in some of the enzymatic processes associated with metabolism. The view that normal metabolism is dependent on the physiological coordination of various active agents in the body is compatible with the various experimental findings on metabolism now available.

HYPERINSULINISM.—This condition results commonly from improper administration of insulin. Occasionally, however, other factors are the cause. Conn (1940) describes three causes: (1) overproduction of insulin due to an adenoma of the pancreas, (2) liver disease preventing normal rapid storage and release of dextrose, (3) an exaggeration of the normal physiological response to food which releases excessive amounts of insulin.

Hyperinsulinism produces hypoglycemic states characterized by weakness, sweating, and dizziness, and even coma and convulsions.

Treatment.—Hypoglycemia caused by hyperinsulinism may be controlled by giving sugar or fruit juice by mouth, or by the intravenous injection of 20 cc., or more, of 25 per cent dextrose. Epinephrine (1 cc. of 1:1,000 solution) given subcutaneously is satisfactory treatment if there is adequate glycogen reserve in the body; but administration should be followed by sugar orally.

Surgical removal of tumor may be indicated if hypoglycemia is due to islet adenoma. If hypoglycemia is due to liver disease, especially biliary cirrhosis, removal of diseased gall bladder may improve liver function. Functional hypoglycemia may be satisfactorily controlled by a high protein, low carbohydrate diet.

HYPOINSULINISM.—Diabetes mellitus is the most common condition associated with inadequate insulin formation. Recently experimental diabetes has been induced by intravenous injection of the drug *alloxan*, which has a selective toxic action on the islets of the pancreas. Thus far, clinical use of alloxan has not proved very successful. Some report alleviation of symptoms.

DIABETES MELLITUS.—Deficiency of the insulin hormone results in diabetes mellitus. The triad consisting of an increase in frequency of urination (polyuria), a great thirst (polydipsia), and an insatiable appetite (polyphagia), together with weakness, constitutes the commonest symptoms manifested in diabetes. The diagnosis of diabetes is not difficult. The presence of marked glycosuria, a highly elevated blood sugar, and acidosis is presumptive evidence and indicates immediate treatment. Since minor degrees of glycosuria are observed in many nondiabetics, it is necessary to exclude other conditions. The *glucose tolerance test* is of great diagnostic value. During this test diabetics show a sustained inability to metabolize sugar rapidly enough to prevent hyperglycemia above 120 mg. per 100 cc. two hours after liberal intake of sugar.

Treatment of Diabetes Mellitus.—Satisfactory treatment consists in the proper administration of insulin and regulation of diet to prevent glycosuria and hyperglycemia, or keep them at a minimum.

The *diet* should be adequate in protein and vitamins, pleasing to the patient, and sufficient in amount to maintain a normal weight.

Insulin Administration.—The aim in the treatment of diabetes is to give insulin in sufficient quantity and manner as to duplicate the function of the normal pancreas in supplying this material. *Amorphous* or *crystal insulins* are rapidly absorbed following subcutaneous injection, causing marked fluctuations and frequent administrations. Attempts to delay insulin absorption resulted in the slowly absorbed product, *protamine insulinate*, prepared by combining insulin with a protamine from fish sperm. Later, a more effective product, protamine zinc insulin, was prepared. This compound is useful in mild diabetes in which a single daily dose suffices to control the disease.

In relatively severe cases, however, doses sufficiently large to control daytime blood glucose may result in hypoglycemia at night. For these cases it has been recommended that two morning injections, one of regular insulin and one of the protamine zinc insulin, be given. To simplify dosage schedules, efforts have been made to add a readily absorbable form of insulin to the zinc protamine insulin.

Other insulin, such as globulin insulin and histone insulin, have been developed to delay action. These preparations have an action intermediate between ordinary insulin and protamine zinc insulin.

Insulin can be purchased in at least four different concentrations. These are designated as U-10, U-20, U-40, and U-80, which means that 1 cc. contains 10, 20, 40 or 80 "units" of insulin.

Mild cases of diabetes mellitus can usually be controlled by diet alone. In average cases the initial dose should be fairly low (10 to 20 units, once or twice daily) and gradually adjusted to the patient's needs. In severe cases 80 units, or more, may be needed and this is adjusted to the patient's needs.

Many methods are used in the administration of insulin. The dose of insulin and method of administration should be adjusted to the needs of the patient. Clinical assays conducted on patients with uncomplicated diabetes reveal that one insulin unit will promote the metabolism of

approximately 1.5 Gm. of dextrose. This gives the physician a guide for insulin administration if he knows how much dextrose the patient will derive from his food and how much insulin the patient himself can provide. The latter may be determined by measuring the patient's ability to utilize carbohydrate without extra insulin. Bethea (1939) gives the following procedure:

"1. The patient is given an ideal diet. After several days' observation, the total amount of sugar excreted daily may be determined and insulin administration commenced beginning with 1 unit of insulin for each 2 grams of sugar excreted. The patient remains on the same diet and the insulin is gradually increased, or diminished, until the amount is determined that will keep the individual sugar-normal.

"2. The patient is placed on an ideal diet. Small doses of insulin are started and the dosage gradually increased until that amount is reached that maintains the individual in the proper state.

"3. The patient is put on a low total, low carbohydrate intake until he becomes sugar-normal. If this is found insufficient to meet the requirements for nutrition and well-being, the diet is gradually increased and at first appearance of glycosuria and hyperglycemia, insulin administration is started; the diet and the insulin are both increased gradually 'stepwise' until the proper amount of each has been determined that will keep the patient in the proper status."

DIABETIC COMA.—This condition, although now encountered in only a small percentage of patients, still remains a problem of importance in therapy. The mortality rate is about 12 per cent. The condition may follow dietary excess, inadequate insulin therapy, nervous shock, hyperthyroidism, and infections.

The symptoms of diabetic coma are attributable to the accumulation of acetone bodies which induces acidosis and reduces the carbon dioxide combining capacity of the blood. The initial symptoms are usually headache, malaise, nausea, vomiting, and pains in the abdomen and extremities. The pulse is rapid, the skin dry, and the pupils dilated. Respirations become long, deep, and rapid, indicative of air hunger. The breath has an acetone odor. Drowsiness, stupor, and coma follow. The blood sugar is greatly elevated, and the urine contains acetone bodies.

Treatment of diabetic coma consists of (1) bed rest, (2) insulin, (3) fluids, and (4) warmth. The initial dose of insulin varies from 20 to 50 units, followed by doses of 10 to 20 units given at one to three-hour intervals until the acetone test is negative.

Dehydration in diabetic acidosis is marked and may be counteracted by the intravenous injection or hypodermoclysis of physiological saline. Gastric lavage, using a 5 per cent solution of sodium bicarbonate, is of value. The early administration of glucose is advocated by some, especially if blood sugar is low and acidosis severe. Later in the treatment the administration of glucose as well as insulin is indicated. Sodium r-lactate, one-sixth molar, is also useful in the treatment of acidosis. This solution may be administered subcutaneously or intravenously. When given by vein administer at the rate of 300 cc. per hour (approx. 60 drops per minute).

Insulin Resistance and Sensitization.—Occasionally, patients manifest a resistance to insulin and in some instances will not respond to 1,000 units or more. There are also infrequent instances of insulin resistance in which patients are very resistant to effects of hypoglycemia by itself. In such persons, unconsciousness cannot be induced in insulin-shock therapy.

Insulin hypersensitivity may be manifested in some patients by a local reaction or a reaction resembling anaphylactic shock. This is caused by some ingredient of the preparation used, e.g., insulin, protamine, etc. All patients should therefore be given small initial doses. Desensitization can be affected by very small doses at frequent intervals.

Insulin Reactions.—Insulin reactions may occur following errors in dosage, irregular food habits, or following excessive exercise. The reaction to insulin is due to hypoglycemia and is accompanied by symptoms similar to hyperinsulinism—mainly fatigue, restlessness, malaise, and weakness. Severe attacks may have additional symptoms, such as pallor, palpitation, tremor and at times severe abdominal pain. Mental disturbances, difficulty of speech, blurring of vision, amnesia and delirium are not uncommon. Severe attacks may end in coma and death.

These symptoms may be relieved by the oral administration of glucose, or, if the patient is comatose, by intravenous injection of 20 to 50 grams of pure sterile dextrose in a 10 per cent solution. If this is not available the administration of diluted corn syrup by stomach tube is indicated. Epinephrine hydrochloride (1:1,000) may be administered subcutaneously in amounts varying from 0.3 to 0.5 cc. These measures should be followed by sugars orally.

Other Uses of Insulin

Insulin Shock Treatment of Schizophrenia.—Insulin has been used with some success in the treatment of *schizophrenia.* Its therapeutic action depends on the production of hypoglycemic shock, a procedure which is dangerous and should be administered with the greatest care and by fully qualified personnel. Obviously it is essential to have available at all times a solution of dextrose suitable for treating the hypoglycemic state.

Treatment consists of daily injections of insulin, starting with from 10 to 20 units, and gradually increasing the dosage until unconsciousness is produced.

Malnutrition.—Insulin has been used in the treatment of nondiabetic malnutrition with reported increase in appetite and gain in weight. Care is necessary to avoid symptoms of hypoglycemia.

Standardization of Insulin.—The U.S.P. method of assay is based on the lowering of blood sugars in rabbits. The International Standard Preparation of Insulin is a crystalline zinc-insulin preparation which contains 22 units of activity per milligram.

Preparations

Insulin Injection, *Injectio Insulini,* U.S.P. (Insulin, Insulin Hydrochloride). An acidified aqueous solution of the active principle of the pancreas which affects the metabolism of glucose. The potency shall be expressed in U.S.P. insulin units which are equivalent in potency to the unit declared on the label of the container of the U.S.P. Zinc-Insulin Crystals Reference Standard. Insulin injection is so standardized that each 1 cc. contains either 20, 40, 80, or 100 U.S.P. insulin units. *Dosage:* To be determined by the physician.

Protamine Zinc-Insulin Injection, *Injectio Zinco-Insulini Protaminati,* U.S.P. A suspension, in a buffered water medium, of insulin modified by the addition of zinc chloride and protamine. *Note:* Protamine zinc-insulin injection differs in its action from that of insulin injection, both in time of onset and duration. To

secure accuracy of dosage the preparation must be brought into uniform suspension by careful shaking before use.

Dosage: Protamine zinc-insulin injection is administered by injection usually into loose subcutaneous tissue. It is never administered intravenously. The dose is to be determined by the physician in accordance with the needs of the patient (U.S.P.). One dose daily, given either before breakfast, before supper, or before retiring, is usually sufficient.

Globin Insulin With Zinc, N.N.R. "Globin insulin (with zinc) is a preparation, in a hydrochloric acid medium, of insulin modified by the addition of globin (derived from hemoglobin of beef blood) and zinc chloride. The quantity of insulin used is such that each cubic centimeter of the finished product contains either 40 or 80 U.S.P. units of insulin." The action is intermediate between that of following regular insulin and protamine zinc-insulin. The period of greatest effect extends from the eighth to the sixteenth hour after injection, almost disappearing at the end of twenty-four hours.

Zinc Insulin Crystals. Zinc insulin crystals are a crystalline preparation of the active antidiabetic principle of the internal secretion of the islands of Langerhans of the pancreas. The crystals contain a small amount of zinc (not less than 0.45 per cent and not more than 0.9 per cent), which is chemically combined with the active principle. Each milligram of the crystals is equivalent to not less than 22 units of insulin. The product is marketed in the form of crystalline zinc-insulin injection.

Lipocaic

Lipocaic has been reported by Dragstedt (1940) and his co-workers as possibly being a pancreatic hormone which prevents fatty degeneration of the liver, observed in depancreatized animals maintained on insulin. These changes can be prevented by the addition of raw pancreas to the diet. Dragstedt and his associates prepared a fat-free extract of pancreas which exerts the same action as the fresh pancreas. This active principle of the preparation has been named *lipocaic.* The significance of this substance in human diabetes is still unknown.

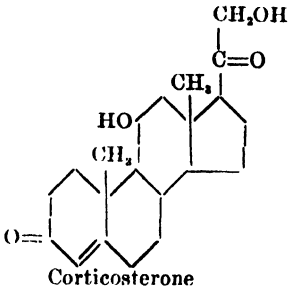
THE ADRENALS

The adrenals are two small yellowish masses of tissue lying above or near the kidneys. Histologically the adrenal gland is composed of two distinct parts, the cortex, or outer layer, and the medullary portion. Although closely associated they have different physiological functions and are of different embryonic origin. The medulla, being derived from sympathetic ganglionic tissue, is of ectodermal origin, the cortex is of mesodermal origin.

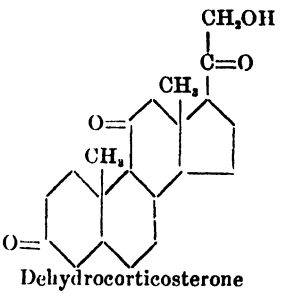
Chemistry.—The chemistry of the active principle of adrenal cortex resembles that of the sex hormones in several ways. There are a number of chemically related compounds obtained from cortical tissue which contains some degree of physiological activity. The following are the structural formulas of three of the active compounds that have been isolated. Desoxycorticosterone is the most active.

Definite progress has been made in the development of new synthetic products which substitute for the adrenal cortex. Synthetic desoxycorticosterone acetate affects sodium and potassium metabolism but not

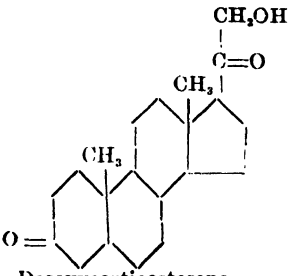
carbohydrate metabolism. Other products, including 11-Dehydrocorticosterone, are being tried clinically. Probably a synthetic product will soon be available that will affect sodium, potassium, and carbohydrate metabolism.



Corticosterone



Dehydrocorticosterone



Desoxycorticosterone

Function of Adrenal Medulla.—The sole function, so far as is known, is the secretion of epinephrine. The secretion follows stimulation of the sympathetic nerves, and the action of this hormone is twofold, i.e., it intensifies the action of the sympathetic nerves and produces the same results as stimulation of these nerves would have produced.

During quiet life there is a question whether any secretion takes place or not. If there is, according to Hoskins (1933), it is below the threshold necessary to stimulate the sympathetic nervous system. Cannon (1940) has advanced the theory that epinephrine serves the organism by aiding in the maintenance of homeostasis in emergencies. During secretion of the hormone or following administration of epinephrine there is, however, constriction of certain arteries, especially those which supply the viscera, relaxation of the smooth muscle of the intestinal tract and bronchi, increased glycogenolysis in the liver and muscle, and many other important actions. See Chapter XIII for detailed account.

Conditions Resulting From Dysfunction.—There are no recognized clinical syndromes of hyper- or hypo-adrenal medullary action save in *paroxysmal hypertension* associated with tumor of the adrenal medulla.

Therapeutic Uses.—The uses of epinephrine are taken up in detail in Chapter XIII.

Function of Adrenal Cortex.—The adrenal cortex produces one or possibly more hormones which are necessary to life. Animals may

live indefinitely with no medullary tissue, but when deprived of all cortical tissue, they promptly die. The following functions are important:

Permeability.—The adrenal cortex plays an important role in the regulation of membrane permeability. Laboratory experiments indicate an increase in cell permeability in adrenalectomized animals. Blood capillary walls show an increased permeability so that blood volume decreases and blood pressure falls. Adrenal extract therapy restores this unbalance, causing a normal plasma volume and normal blood pressure.

Pigmentation.—The pigmentation characteristic of Addison's disease may be due to a disturbance in enzyme action. Adrenal extract therapy sometimes causes a disappearance of this discoloration.

Metabolism.—There is some question whether the basal metabolic rate in Addison's disease is subnormal or not. The metabolic disturbances present may be explained on the basis of circulatory and nervous system changes. Reduction in enzyme activity may be a factor.

Electrolytic Disturbances.—The most common changes in electrolytes are the loss of sodium and retention of potassium by the kidney. There is also an increase of potassium in erythrocytes and in skeletal muscle cells and a shift of potassium from the liver and heart. Adrenal extract therapy to adrenalectomized animals reestablished normal potassium relations.

Carbohydrate Changes.—Patients with Addison's disease evidence an apparent reduction in carbohydrate absorption. With this reduction there is a possible increase in utilization. There is also a diminished ability to form carbohydrate from noncarbohydrate sources. These conditions tend to lower the liver glycogen, a condition which is remedied by large doses of adrenal extract, corticosterone, and dehydrocorticosterone.

Nervous System.—Nervous system disturbances, such as insomnia, restlessness, mental fatigue, and sensory changes, appear early in Addison's disease.

Addison's Disease

Addison's disease is the most common condition resulting from insufficiency of the adrenal gland usually caused by tuberculosis, tumor, hemorrhage, or atrophy. The condition is characterized by profound asthenia, hypotension, gastrointestinal disturbances, pigmentation, anemia and cachexia. Diagnosis is often difficult because of the numerous other causes which give rise to one or more of these symptoms. Laboratory findings consist of lowered blood calcium and elevated potassium, increased blood urea or nonprotein nitrogen, and marked reduction in blood volume. The areas of pigmentation seen in Addison's disease are due to excessive accumulation of the normal cutaneous pigment melanin.

Treatment.—Therapy of this condition consists in the restoration of the normal state by the administration of water, salt, sugar, and its maintenance by use of substitution hormone therapy.

In *mild cases* of the disease, the administration of large amounts of sodium chloride (6 to 10 Gm.) may suffice. If symptoms permit, hormone therapy, such as suprarenal cortex extract (cortin) 10 to 20 cc. daily divided in two or three doses and given subcutaneously, is indicated.

Desoxycorticosterone acetate is a satisfactory agent for ordinary maintenance in Addison's disease. It is only a partial substitute, being potent in the sodium-retaining action but ineffective in carbohydrate

disturbances. *Overdosage* may cause edema and heart failure. The dosage varies from 2 to 10 mg. intramuscularly daily. Not more than 5 Gm. of salt should be administered daily with desoxycorticosterone.

Pellets of desoxycorticosterone acetate when implanted subcutaneously produce a prolonged effect, but unexpected rapid absorption may cause toxic symptoms. Desoxycorticosterone in a propylene glycol solution has been administered under the tongue with favorable results.

Treatment of Addison's Crisis.—Place patient in a quiet, dark room. Administer by vein an infusion of 10 per cent dextrose. (Continue infusion, giving 3 or 4 liters over several hours.) Immediately give a subcutaneous injection of 50 to 75 c.c. of suprarenal extract or 5 to 25 mg. of desoxycorticosterone. Give large amounts of fluid by mouth, and continue dextrose and hormonal therapy as indicated by progress of patient. Recovery usually occurs in about twenty-four hours; then return patient to ordinary treatment.

Other Uses: Both cortex extract and desoxycorticosterone have been employed extensively in serious burns and following surgery. Unrelated to the adrenals it has also been used in small doses in conditions of weakness and low blood pressure. The results of therapy in these conditions are of little consequence.

Standardization of Adrenocortical Preparations.—No official standard is available. These preparations are standardized on adrenalectomized animals. Potency may be expressed in the dog unit—the minimum daily dose per kilogram of body weight necessary to maintain a dog for a period of from seven to ten days without loss of body weight and evaluation of nonprotein nitrogen in the blood.

PREPARATION

Sterile Solution of Adrenal Cortex, N.N.R.

Desoxycorticosterone Acetate, *Desoxycorticosteroni Acetas*, U.S.P. $C_{23}H_{32}O_4$. *Dosage:* Intramuscular and implantation—as determined by the physician according to the needs of the patient (U.S.P.).

SEX HORMONES

The growth and development, and also the functioning, of the sex organs are under the control of various sex hormones. We can rightly say that all the hormones are necessary for the normal development and function of the reproductive system. These substances act by their stimulating and inhibiting and, one might well say, correlating effects on the reproductive system. In this discussion all hormones produced by the gonads or which exert their chief action on the reproductive system will be classified as sex hormones.

The *sex hormones* of special importance at the present time are:

A. Anterior Pituitary
   1. Pituitary Gonadotropic Hormones
      a. Follicle-Stimulating Hormone (Prolan A)
      b. Luteinizing Hormone (Prolan B)
   2. The Lactogenic Hormone (Prolactin)

B. Gonadotropic Hormones From Sources Other Than the Pituitary
   1. Chorionic Gonadotropic Hormone
   2. Equine Gonadotropic Hormone

C. Ovarian Hormones

Natural Occurring Estrogens

a. Estrone
b. Estriol
c. Estradiol

Synthetic Estrogens

d. Diethylstilbestrol
e. Hexestrol
f. Benzestrol
g. Mestilbol
h. Ethinyl estradiol

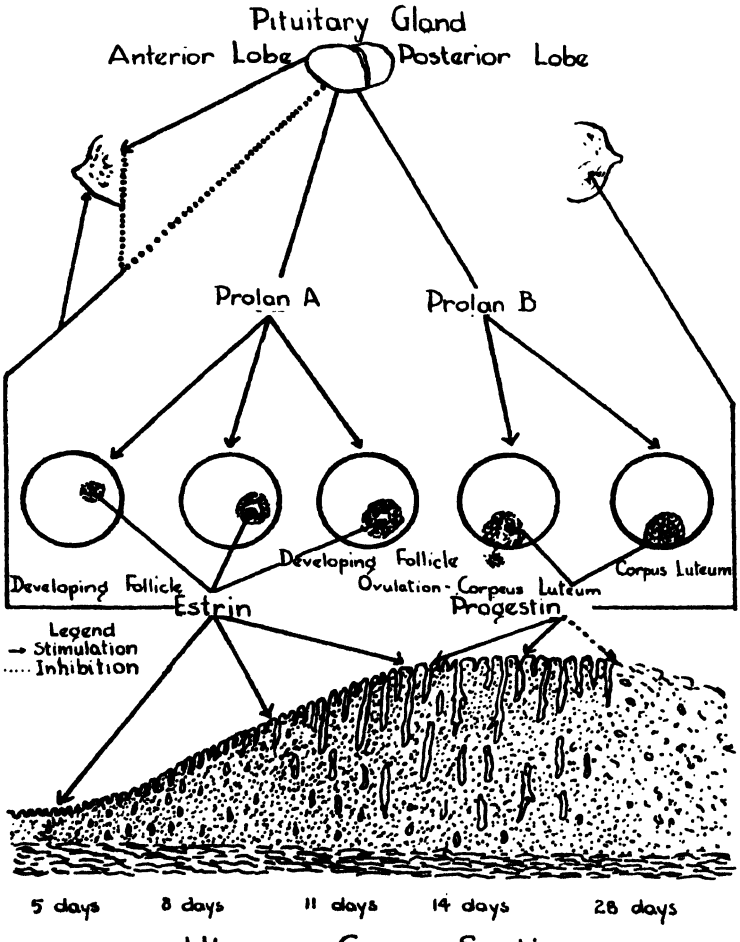


Fig. 35.—Interrelationship of the sex hormones.

2. Progestational Compounds
   a. Progestin (Natural)
   b. Progesterone (Synthetic)
   c. Pregnendione (Synthetic)

D. Male Sex Hormones
1. Androsterone (Natural)
2. Testosterone (Synthetic)
   a. Testosterone Propionate
   b. Methyltestosterone

A. Anterior Pituitary

Zondek sums up the importance of the anterior pituitary sex influences as follows:

"Without the anterior lobe hormone, no gonad activity! no ovulation! no sex rhythm! Without the anterior lobe, atrophy of the sex mechanism! Without the anterior lobe, no conception!"

In addition to its other controlling activities the anterior pituitary body is the "master gland" of gonad function. Its removal in the immature animal or its failure to develop arrests the growth and development of the gonads and accessory organs. In the adult it results in the atrophy of the gonads, in both the male and the female, with the disappearance of sex instincts and cessation of ova and spermatozoa production. That these results are due to lack of hormones normally secreted by the pituitary is demonstrated by the fact that injection of pituitary extracts restores these organs to their normal condition.

Pituitary hormones (genuine), the two gonadotropic hormones, and the hormone from the serum of pregnant mares, all tend to stimulate ovarian function. Pituitary hormones administered by vein are somewhat dangerous, due to the protein content, while the concentrated preparation from the serum of pregnant mares is essentially protein-free. Once the follicle has been made to ovulate, and the corpus luteum has been formed, pituitary stimulation is still required to sustain the action of the corpus luteum (Hisaw, 1935); therefore continued treatment with the gonadotropic hormone is recommended to maintain luteal activity.

The interrelationship between the sex hormones is shown in Fig. 35.

Pituitary Gonadotropic Hormones.—The exact number of gonadotropic principles is a matter of controversy. Most observers now accept the existence of two separate factors: the follicle-stimulating (prolan A) and the luteinizing (prolan B) hormones.

Follicle-Stimulating Hormone (F.S.H.).—This substance produces rapid prepubertal development. After puberty it effects follicle ripening, maturation of ova, estrus (or menstruation), and uterine hypertrophy. Acting with the luteinizing hormone, it produces completion of estrus or the full development of premenstrual endometrium. Both hormones act upon the uterus indirectly through the ovary. (See Fig. 35.)

This hormone is prepared from animal pituitary glands, urine of menopausal or castrate women, and pregnant mare's serum.

Luteinising Hormone (L.H.).—This substance produces hyperluteinization, retention of many ova (which become cystic), suppression of estrogen by high blood progesterone (hormone of corpus luteum). It stimulates the interstitial (Leydig) cells in the male, setting free male sex hormone. It also tends to cause atrophy of the seminiferous tubules and penis, loss of libido, and sometimes loss of fertility.

The actions of the gonadotropic hormones of the anterior pituitary may be summarized as follows:

Follicle-stimulating hormone	Ripening of follicles, small corpora lutea. Production of estrin, phenomena of estrus. Proliferation of epithelium of seminiferous tubules of testes.
Luteinizing hormone	Extensive luteinization. Retained ova. Production of corpus luteum hormone. Inhibition of estrin, producing suppression of estrus. Stimulation of interstitial tissue of testes.

SUMMARY.—The gonadotropic hormones of the anterior pituitary preside over the development and function of the reproductive system as well as over secondary sex characteristics in both sexes. In the female the follicle-stimulating hormone matures the graafian follicle while the luteinizing hormone stimulates the corpus luteum, causing production of the ovarian or secondary hormones, folliculin and progestin, which regulate the menstrual cycle and implantation of fertilized ovum.

In the male the gonadotropic hormones stimulate descent, development, and function of the testes.

Therapeutic Uses of Pituitary Gonadotropic Hormones.—Theoretically one might expect wide clinical use of the gonadotropic hormones, but at present they are little used clinically. Their use has been handicapped by the lack of pure preparations of individual gonadotropic hormones. It may soon be possible to have separate preparations of each for clinical trials. Their practical application has been further hindered by the presence of proteins in many of the commercial preparations which may cause painful local reactions and occasionally allergic reactions.

Conditions in which gonadotropic extracts have been used with some success include: Fröhlich's syndrome (dystrophia-adiposogenitalis), hypogenitalism, amenorrhea, menometrorrhagia, sterility, and cryptorchidism. Mazer (1941) found these substances ineffective in functional menstrual disorders.

Sterility.—Great interest has developed in the subject of sterility. The male is sterile in about 20 per cent of infertile marriages. Stimulation of spermatogenesis in patients with secondary hypogonadism is not very satisfactory. It may be possible to cause some stimulation with some of the newer *pituitary gonadotropins* in powder form.

Lactogenic Hormone.—This factor causes lactation in animals whose mammary glands have previously been subjected to the influence of appropriate amounts of ovarian hormones. Since lactation ceases following removal of the pituitary, and pituitary extracts have the capacity to cause enlargement of the mammary glands and stimulate the secretion of milk in nonparturient animals, it has been suggested that the pituitary secretes a specific lactation hormone. The ovarian hormones are responsible for the growth of the mammary glands, while the lactogenic principle (prolactin) is probably responsible only for lactation. The continuation of lactation, however, is also dependent upon the intact nervous connection of the mammary glands. Milk secretion is also dependent to some extent on the stimulus of sucking.

There is some evidence to indicate that prolactin is useful in causing increased milk production when used in the human female. At present prolactin is of little or no value clinically.

B. Gonadotropic Hormones From Sources Other Than the Pituitary

Chorionic Gonadotropic Hormone.—The gonadotropic substance excreted in the urine of pregnant women is a water-soluble substance, a glycoprotein containing about 12 per cent of galactose.

The chorionic gonadotropin differs from preparations from the anterior pituitary in that it has little or no follicle-stimulating effect on the ovaries of primates, and it may actually cause degenerative changes. In addition, this substance is unable to stimulate any endometrial responses, which indicates conclusively the inability of this substance to stimulate the growth of normal ovarian structures.

This chorionic gonadotropin acts also on the male reproductive organs. Chronic gonadotropin is a satisfactory agent for stimulation therapy and testosterone propionate for substitution therapy in hypogonadism. Chorionic gonadotropin will produce maximum stimulation of function only when the testes are capable of showing maximum response to stimulation. Persistent hypopituitarism may so damage the testes that no response occurs from stimulation. Under these circumstances testosterone propionate is indicated. In treatment, the age at which it is instituted is of vital importance. Start treatment at the age at which puberty normally sets in, in order to secure maximum growth of genitalia and to prevent skeletal abnormalities.

Therapeutic Uses.—The anterior pituitary-like (human chorionic gonadotropin) hormone from pregnant women has a limited field of usefulness in endocrine therapy of women since it has little effect on human ovaries. This preparation has had wide use in functional ovarian disorders in the past, but the early enthusiasm for its use has waned in recent years. It has been shown recently that beneficial responses in functional bleeding are no more common with this substance than with estrogen or progesterone, indicating that this substance has no specific value. It is claimed that *pubertal bleeding* is responsive to this therapy. It should be administered every two or three days for one or two months. If no benefit is obtained the treatment should be stopped since there is a possibility of harming the ovaries. Considerable disagreement exists among the various investigators regarding the type of bleeding benefited by chorionic gonadotropin obtained from the urine of pregnant women.

The chorionic gonadotropin from human pregnancy urine has been used widely in the treatment of *cryptorchidism* where there are no anatomic barriers causing obstruction of the testicular descent. The diagnosis of an anatomic lesion can often be made in this manner where the therapy fails. *Dosage:* The usual dose in treating cryptorchidism is from 200 to 500 international units two to three times a week. Long-continued injections may be dangerous and treatment should not be maintained after eight weeks in the absence of progressive descent. Therapy should be discontinued on the development of signs of precocious maturity.

Preparations

Follutein, N.N.R. The water-soluble gonadotropic substances obtained from urine of pregnant women.

Korotrin, N.N.R. The water-soluble gonadotropic substances obtained from urine of pregnant women.
Lyovac Chorionic Gonadotropin, N.N.R.
Chorionic Gonadotropin, N.N.R.

Equine Gonadotropic Hormone.—A rich source of gonadotropic hormone was found in 1930 by Cole and Hart in the blood serum of pregnant mares. This hormone produces effects similar to those achieved by extracts of the anterior pituitary gland. Thus it is capable of stimulating germinal epithelium of testes and ovaries in animals; it can produce fertile ovulation in rats, cows, and pigs; it can induce ovarian growth in primates. A number of investigators report production of ovulation in human beings by means of this gonadotropic hormone. It has a prolonged action since it is metabolized very slowly in the body and is not excreted by the kidney.

Therapeutic Uses.—The gonadotropic hormone from pregnant mares' serum has a stimulating action on virtually all phases of ovulation and testicular activity. Thus it would seem to be applicable in therapy whenever gonad stimulating therapy is indicated. While experimental findings would indicate a usefulness in hypo-ovarianism, clinical trials have as a whole been disappointing. Hamblen and his associates believe that good results are obtained by giving equine gonadotropin during the first half of the menstrual cycle to cause follicle growth and ovulation, then administering chorionic gonadotropin during the second half to promote luteinization.

The gonadotropic hormone has been recommended for various conditions such as *amenorrhea, functional bleeding, dysmenorrhea, sterility, cryptorchidism,* and *delayed sexual development.*

The therapeutic objective in *amenorrhea* is to induce follicle maturation and ovulation by stimulating ovarian activity. The recommended dosage of gonadotropic hormone is 200 international units on alternate days for a period of fourteen days. Repeat series after a rest of two weeks. *Functional bleeding* is frequently due to a persistent follicle, which leads to a proliferative type of endometrium. Through the influence of this hormone, ripening of the graafian follicle is encouraged. Administer 600 to 1,200 international units (I.U.) at the onset of flow, or in divided dosage of 200 to 400 I.U. three times during the week preceding the first day of menstruation. When *dysmenorrhea* is considered due to deficiency of the follicular hormone (as determined by a lowering of the blood serum level of estrogenic substance) gonadotropic hormone is recommended. It acts through follicular stimulation.

Equine chorionic gonadotropin offers considerable promise in the relief of *sterility* attributable to failure of normal ovulation. It acts by supplying the deficient follicle-maturing stimulus. The recommended dosage is 200 I.U. given on alternate days for the first ten days of the cycle, or daily from the seventh through the twelfth day. The last dose of either series should be somewhat larger—400 to 600 I.U. This gonadotropic hormone in favorable cases not only produces descent of the testes but also alleviates the associated signs of hypogenitalism—reduction of pelvic fat, increase in size of the testes and penis, and the appearance of secondary sex characteristics. Therapy should be continuous for prolonged periods. Some recommend 200 I.U. of hormone three times a week for several weeks, interrupted by an occasional rest period of two weeks. The dosage may be increased to 400 I.U., three times a week, if indicated. In the treatment of *delayed puberty* in girls continuous therapy is recommended.

Standardization.—International standard preparations are available for assay of both chorionic and equine gonadotropins; 0.1 mg. of the International Standard of chorionic gonadotropin and 0.25 mg. of the International Standard of equine gonadotropin contain one unit of chorionic and equine gonadotropin, respectively. Assay is based either on direct morphologic changes in the gonads or in secondary changes in the accessory sex organs.

C. Ovarian Hormones

During the last forty years physiologists and chemists have made remarkable strides in elucidating the role played by the ovary in the mammalian organism. It has been firmly established that in addition to producing ova, this gland controls the development and maintenance of the female reproductive tract and permits the initiation and continuation of pregnancy. Further, it has been clearly demonstrated that the ovary is directly under the control of certain secretions of the anterior lobe of the pituitary gland, and that the ovary in turn exerts its control over the reproductive tract by secreting certain hormones.

The ovaries produce hormones which are essential for the proper functioning of the uterus, particularly for the production of cyclic growth processes of this organ and for the development of the decidua. In addition, these hormones determine cyclic changes in the growth of the mammary gland. It is believed that in addition to intrinsic factors situated in the ovary itself, hormones elaborated by the anterior pituitary regulate the growth of the follicles, ovulation, and corpus luteum formation.

Estrogens

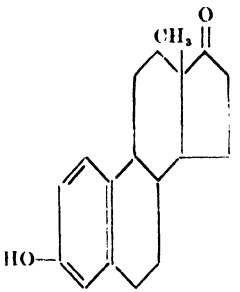
The estrogens are substances which produce estrus. They are widely distributed, being obtained from both plant and animal sources; estradiol synthetic preparations are also available.

Three natural estrogens are available in crystalline form: *estradiol,* obtained from ovaries and pregnancy urine; *estriol,* obtained from placental tissue and pregnancy urine; and *estrone,* obtained from the urine of pregnant mares. Preparations of estrogens "solutions of estrogens" are prepared from pregnant human or pregnant mare urine. They are noncrystalline and their activity is primarily due to their estrone content.

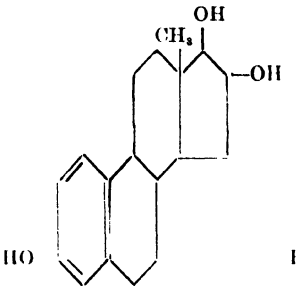
Action of Estrogenic Hormones.—Estrogenic hormones are capable of: (1) producing "estrin withdrawal bleeding"; (2) generating an intermenstrual type of endometrium; (3) inducing growth of the hypoplastic uterus; (4) relieving the symptoms of the menopause; (5) converting a "menopausal" into an "estrous" type of vaginal smear; (6) restoring the normal appearance of the vulva and vagina when these have become atrophic as the result of the estrogenic deficiency of the climacteric; (7) causing painful swelling of the breasts; (8) influencing proliferation and activation of the epithelium of the mammary glands; and (9) relieving the pain of dysmenorrhea.

The injection of potent estrogenic substances will produce in castrate animals changes in the accessory sex organs which are typical of estrus. Long-continued administration will, however, induce hyperplastic and metaplastic changes in the uterus and breast. Some observers believe that clinical endometrial hyperplasia, chronic cystic mastitis, and fibromyomas are due to long-continued estrogen secretion by the ovaries.

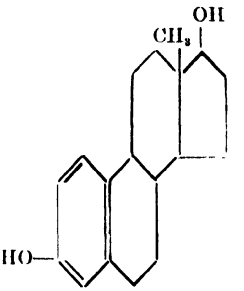
Estrogenic substance is also responsible for the contractility of the uterus and the sensitivity of the myometrium to oxytocic agents. The smooth muscle of the Fallopian tube also responds to estrogens.



Estrone

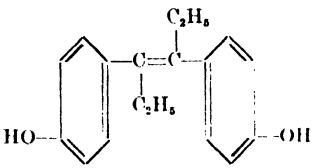


Estriol

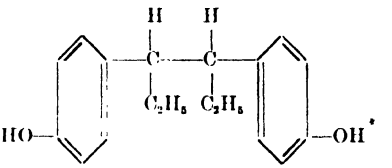


Estradiol

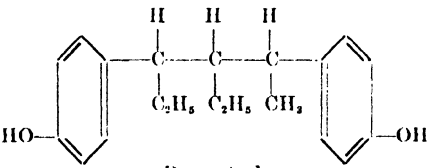
Naturally Occurring Estrogens



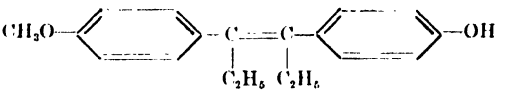
Diethylstilbestrol



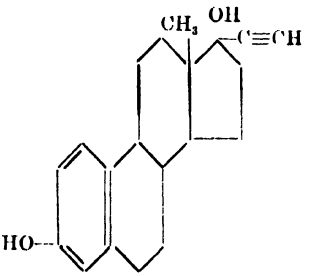
Hexestrol



Benzestrol



Mestilbol



Ethinylestradiol

Synthetic Estrogens

Excretion of Estrogens.—The excretion curve of estrogens in the normal menstruating woman is irregular and varies from day to day. There is generally a peak at the height of follicular activity and another before menstruation. During pregnancy estrogenic substances are excreted in increasing amounts through gestation and for several days after delivery, much of the estrogenic material is excreted in a combined form of glycuronates which are inactive physiologically.

A number of synthetic estrogenic hormones are available for clinical use. These preparations are active orally and are reported to be more toxic than the natural product. Their toxicty is of little clinical importance provided they are administered properly. The cheapness of these substances has been a great boom to many women suffering from disorders associated with ovarian insufficiency.

Toxicology.—Diethylstilbestrol is representative of the group of estrogens. Its toxicology is given. Overdosage of diethylstilbestrol will produce toxic symptoms which can be attributed to exaggerated estrogenic action. These include nausea and vomiting, the production of uterine bleeding during continuous therapy, painful breasts, and vaginal irritation. The occurrence of nausea and vomiting is apparently dependent in part on dosage of diethylstilbestrol and may be controlled or the incidence reduced by employing minimum effective dosages. When moderate doses (1 mg. or less daily) are given intermittently, unpleasant reactions are infrequent (MacBryde, 1941). Blood studies and liver function tests have failed to provide definite evidence of toxicity to these organs. The administration of large quantities of stilbestrol over long periods of time have failed to reveal toxic effects on the blood and urine. In cases that came to autopsy, liver, kidneys, and adrenals showed no change that could be attributed to stilbestrol (Davis, 1940).

Diethylstilbestrol is a powerful new synthetic drug, and caution must be employed in its use. Patients receiving the drug should be under continuous medical supervision. The breasts and pelvic organs should be examined before treatment and at intervals during therapy. It is often advisable to check the physiologic estrogenic effect of the therapy by vaginal smears. In the treatment of menopause, however, relief of symptoms is usually sufficient evidence of the success of treatment.

Therapeutic Uses of Estrogens.—Estrogens are used as substitution therapy in primary disorders of, defects in, or insufficiency of, ovarian function. They are especially useful for relief of symptoms associated with natural or surgical menopause and for the relief of senile or menopausal vaginitis. Estrogens are useful in the suppression of lactation. They have been used with success in temporarily arresting prostatic carcinoma when surgical castration is contraindicated. Estrogen therapy also has been used with success in postcastration symptoms in the male.

Menopause

The menopause is the period of change accompanied by cessation of ovarian activity in women. It may be characterized by nervousness, sweating, and hot flashes.

In the treatment of menopause an effort should be made to administer the minimum amount of estrogen that will control symptoms without inducing uterine bleeding. Slight spotting which occurs periodically is not serious. Treatment should be discontinued until it disappears and then resumed. In cases with prolonged and excessive bleeding, it is best to discontinue treatment permanently. Patients with fibroids and carcinoma of the cervix or fundus should not be given estrogen therapy.

Treatment.—Symptoms may be alleviated by sedatives, and severe cases may be benefited by estrogenic therapy. Diethylstilbestrol may be given in doses of 0.10 to 1 mg. daily. Most clinicians are in agreement with Novak (1944) that only rarely is a larger dose than 0.1 mg. of diethylstilbestrol needed.

The other estrogens may also be used, hexestrol in dose of 1 mg., benzestrol in dose of 3 mg., daily. The natural estrogens may also be used—estriol, 60 to 120 mg., three times daily, orally; ethinyl estradiol, 0.05 mg. daily, orally; or estrone or estradiol benzoate, 1 mg. intramuscularly one to three times a week.

Recommended dosages of diethylstilbestrol are found in Table XXXI. *Keep dosage at the minimum necessary for relief.*

TABLE XXXI

RECOMMENDED DOSAGE OF DIETHYLSTILBESTROL, TO BE ADJUSTED TO INDIVIDUAL REQUIREMENTS

	BY MOUTH	AS VAGINAL SUPPOSITORY	BY INJECTION
Menopause	0.1 to 1 mg. daily	0.5 mg. daily	0.5 to 2 mg. 2 to 3 times weekly
Senile Vaginitis	0.1 to 1 mg. daily	0.5 mg. daily	0.5 to 2 mg. 2 to 3 times weekly
Gonorrheal Vaginitis	20 mg. total given over 1 to 3 weeks	0.1 mg. daily for minimum of 3 weeks	No recommendation
Suppression of Lactation	5 mg. 1 to 3 times daily for a total of 2 to 4 days		5 mg. once or twice daily for a total of 2 to 4 days

SENILE VAGINITIS

The menopause may be complicated by a thinning of the vaginal and perineal epithelium accompanied by intensive itching. *Treatment:* Treat as outlined for menopause. Local application of estrogen suppositories may be indicated to supplement systemic therapy.

Estrogens found a wide use in the treatment of *gonorrheal vaginitis in children* before the advent of the sulfonamides. The estrogens produce a cornified epithelium and an acid reaction in the organs unsuitable for growth of bacteria.

MENORRHAGIA AND METRORRHAGIA

Menorrhagia means prolonged or profuse flow, and metrorrhagia means flow at irregular intervals between periods.

Treatment: Obviously, hormone therapy should be instituted only after a careful diagnosis eliminating other causes of bleeding. Sex hormone therapy is reported to be of use in treatment. Smith (1944) of the Harvard Medical School recommended the following procedure:

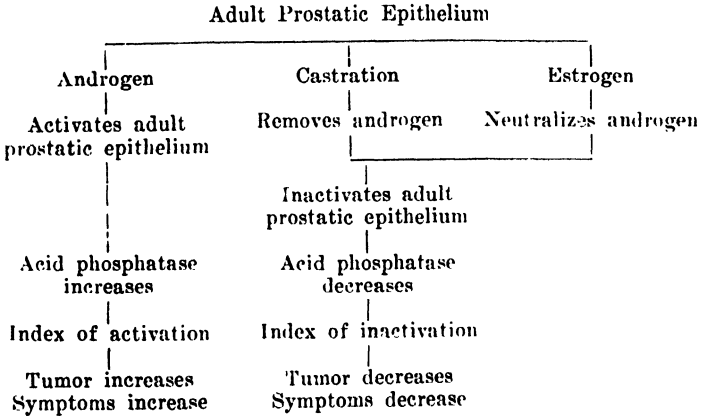
To those who bleed regularly but too profusely or too long, give 10 mg. of progesterone and 1 mg. of estradiol intramuscularly on the twenty-first day and follow on the twenty-second to the twenty-fifth day by 10 mg. of progesterone intramuscularly; three cycles of this

therapy are usually sufficient. For those whose periods are occurring too frequently, the same procedure is used, beginning the injections eight days before the anticipated onset of flow and continuing until the cycle lengthens. For those having a continuous flowing, Smith advised the immediate intramuscular injection of 10 mg. of progesterone and 1 mg. of estradiol and then of 10 mg. of progesterone daily for the next four days. He said that during this time the bleeding will probably decrease or cease and that two to four days later a fairly normal period will occur. Counting the beginning of this period as the first day, he would have the injections repeated beginning on the twenty-first day. Treatment of this sort, he said, should be given at least twice, and it may be required again after a lapse; if the patient is bleeding profusely, the daily dose of progesterone may even be raised to 50 mg. for a time. Cuyler, Hamblen, and Davis (1942) employ diethylstilbestrol by mouth in daily doses ranging from 2 to 6 mg. in place of estradiol.

Prostatic Carcinoma

Diethylstilbestrol causes a regression of the primary growth and relief of pain. However, the results are not as striking as with castration. Some favor castration and reserve diethylstilbestrol therapy for those who show evidence of extragonadal activity or refuse castration.

The suggested relationship between gonadotropic substance and prostatic epithelium is shown below. Androgen activates the prostatic or tumor cells. This activation may be measured by the serum acid phosphatase. Castration and the removal of the androgen cause a drop in the index of activation acid phosphatase, and we see clinical signs of regression of the tumor.



Dosage.—Some observers recommend the oral administration of 1 mg. of diethylstilbestrol three times daily for a period of two to three weeks. Then 2 mg. once daily for three or four weeks, this reduced to 1 mg. daily indefinitely.

Other Uses of Estrogens

Estrogen in oil, applied with a nasal atomizer, has been used in the treatment of *atrophic rhinitis.* The stimulating effect of estrogens in promoting growth of epithelial mucosa is the basis of

this treatment. Estrogens have been used in the treatment of *cystic mastitis* and painful breasts, and for promoting the growth of the breasts. Their use in these conditions is still in the experimental stage.

Suppression of Lactation.—It is frequently desirable to cause cessation of lactation after normal or abnormal parturition. The hormonal method is convenient. Estrogens, administered intramuscularly or orally in dose of 2,000 I.U. twice daily for three to five days are usually sufficient if therapy is started early. If engorgement has set in, 10,000 I.U. administered intramuscularly for two to three days may be indicated.

Danger of Inducing Cancer.—Large doses of estrogens have been shown to increase the incidence of cancer in susceptible animals. Whether this holds true in women treated with estrogens is questionable. Novak (1944) said that it is the consensus that the clinical employment of estrogens in the customary therapeutic dosage presents no hazard, but prolonged use of these substances is contraindicated in persons suffering from cancer or who have a familial history of cancer. This alone is one potent argument against the use of proprietary cosmetics containing estrogenic substances.

Standardization.—International Standard preparations of estrone and estradiol monobenzoate are available—each unit of activity is 0.1 microgram.

Assay methods commonly used are based on the examination of vaginal smears in rats and mice and on the weight increase of the uterus of castrated rats.

Preparations

Estriol, N.N.R. (Theelol), Orally, 0.06 to 0.12 mg. from one to four times daily, alone or as supplement to parenteral therapy.

Estrone, *Estronum,* U.S.P. (Theelin, Oestrone). *Dosage:* 1 mg. (1/60 grain).

Estrogenic Substances (Water Soluble) N.N.R. Largely estrone. 1,000 to 10,000 units.

Estradiol, *Estradiol,* U.S.P. (Dihydrotheelin, Oestradiol). *Dosage:* 0.2 mg. (1/300 grain).

Estradiol Benzoate, *Estradiolis Benzoas,* U.S.P. (Oestradiol Benzoate). *Dosage:* 1 mg. (1/60 grain), once or twice weekly, intramuscularly in oil solution.

Benzestrol, N.N.R. *Dosage:* 2 to 5 mg.

Hexestrol, N.N.R. *Dosage:* 2 to 3 mg.

Ethinyl Estradiol, N.N.R. *Dosage:* 0.5 mg.

Mestilbol, N.N.R. *Dosage:* 0.5 to 1.0 mg.

Diethylstilbestrol, *Diethylstilbestrol,* U.S.P. *Dosage:* 0.5 mg. (1/120 grain).

Diethylstilbestrol Capsules, *Capsulae Diethylstilbestrolis,* U.S.P. *Dosage:* 0.5 mg. of diethylstilbestrol (U.S.P.), usually available in capsules containing 0.5 and 1.0 mg.

Diethylstilbestrol Injection, *Injectio Diethylstilbestrolis,* U.S.P. A sterile solution of diethylstilbestrol in oil or other suitable solvent, containing about 100 per cent of the labeled amount of the drug. *Dosage:* Intramuscularly, 0.5 mg. of diethylstilbestrol (U.S.P.), usually available in ampuls containing 0.5 or 1 mg. in 1 cc.

Diethylstilbestrol Tablets, *Tabellae Diethylstilbestrolis*, U.S.P. *Dosage:* 0.5 mg. of diethylstilbestrol (U.S.P.), usually available in tablets containing 0.1, 0.5, and 1.0 mg.

Numerous other useful preparations, including suppositories, preparations in oil, etc., are described in detail in the N.N.R.

Progestational Compounds

(Corpus Luteum Hormones)

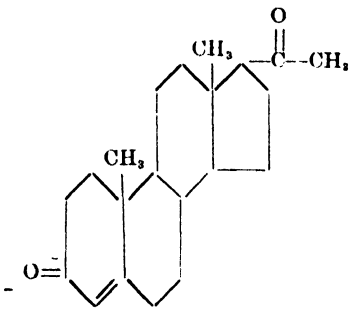
The endocrine function of the corpus luteum is now well understood. The gland is part of the mechanism of pregnancy (corpus luteum forms in the follicle after the ovum begins its journey down the Fallopian tube); it delivers into the blood stream a substance called progesterone or progestin, which has the property of inducing development of the endometrium, preparing the uterus for reception of the ovum, and nutrition of the embryo.

The hormone of the corpus luteum is available in the form of *progestin*, a crude extract of ovarian tissue, and also as the pure crystalline hormone *progesterone*. In 1939 *pregneninolone*, a substance closely related to progesterone, was found to be effective when given by mouth. Pregneninolone is androgenic as well as progestational in its action, according to Emmons and Parker. They have shown that this substance will induce growth of the uterus without preliminary treatment by an estrogen, which is necessary in the case of progesterone. Pregneninolone has been used clinically with promising results.

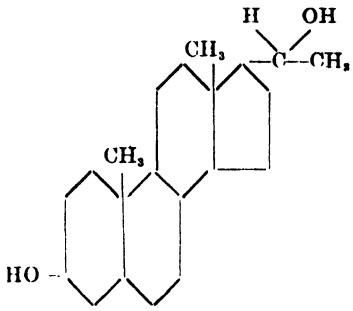
Chemically progesterone is closely related to the estrogenic and testicular hormones. It can be prepared by oxidizing cholesterol. This method now serves for its commercial preparation. Human pregnancy urine contains two isomeric pregnanediols designated as pregnanediol. Pregnanediol is thought to be derived by reduction of progesterone, a view supported by the fact that it can be transformed into this hormone by oxidation.

Actions of Progesterone.—The hormone of the corpus luteum, progesterone, changes the uterine mucosa to a glandular or secretory type in preparation for nidation of the fertilized ovum. If fertilization does not occur, the corpus luteum degenerates, withdrawing the progesterone influence, and menstruation occurs. When fertilization of the ovum occurs, the corpus luteum persists throughout the greater part of pregnancy and its hormone, progesterone, continues to exert its protective action on the uterus. Besides the effects mentioned, the hormone has been shown to inhibit uterine motility and to suppress menstruation, and to cause acinar development of the breast tissue. Although progestin, the crude extract of the corpus luteum, has the capacity of duplicating the action of corpus luteum, progesterone, the pure hormone, frequently requires the addition of estrogen in order to reproduce the action of the corpus luteum. The effectiveness of progestin is apparently due to the fact that crude extracts contain a sufficient amount of estrogen.

Pregnanediol, derived from progesterone, represents the latter's secretion product in the urine. It appears in the urine conjugated with glycuronic acid to form a water-soluble compound, sodium pregnanediol glycuronidate. The curve of pregnanediol excretion parallels the rise, activity and retrogression of the corpus luteum and is a rough measure of the functional activity of the corpus luteum.

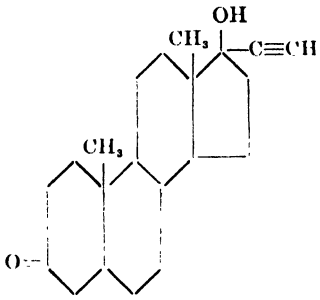


Progesterone



Pregnanediol
(Inactive urinary excretion product of progesterone)

Naturally Occurring Progesterones



Pregneninolone
(Ethinyltestosterone)

Synthetic Progesterones

Therapeutic Uses.—Although progesterone therapy may still be considered in the experimental stage, physicians who follow the instructions of the more critical clinical investigators have found it useful in such conditions as *abortion, dysmenorrhea, after-pains* of early puerperium and in *metrorrhagia* and *menorrhagia.*

In many cases of *threatened* or *habitual abortion,* due to premature withdrawal of the corpus luteum hormone, the supplementary administration of progestin or progesterone will maintain pregnancy through the critical period by maintaining the endometrium in the proper state for nutrition of the embryo and by sedative action of the uterine musculature. *Dosage:* In treating *threatened* or *habitual abortion,* 1 to 5 mg. of progesterone are injected daily from the beginning of pregnancy, with a gradual reduction in dose until the fourth month when therapy is stopped (Grollman, 1941). In cases of habitual abortion progestin given hypodermically in doses of 5 units every other day until viability of the fetus has proved most effective (Mazer, 1941). If progestin is used, one international unit is 1 mg. progesterone. These

preparations are in oil solutions for intramuscular injection. The experienced clinician has learned to supplement progesterone with vitamin E as well as thyroid medication. Certain antispasmodics may also be of value to depress uterine contractions.

The use of progesterone in *dysmenorrhea* has been advocated on the assumption that the disorder is due to hypermotility of the organ. Doses of 1 to 3 mg. daily, intramuscularly, for a few days preceding menstruation are recommended. Pregneninolone, administered by mouth, in doses of 5 mg., has been reported as efficacious.

After-Pains.—Pains due to uterine contractions following parturition are promptly relieved by 1 international unit of progesterone, or progestin. In addition to inhibiting uterine contractions it appears that this treatment diminishes pain by preventing an ischemic condition of the uterus during a portion of its contraction phase. No harmful effects have been reported following this treatment.

Metrorrhagia and Menorrhagia.—Favorable results have been reported following progestin therapy in these conditions. The rationale for the use of progestin in these conditions rests on the following observations: (1) That corpus luteum is present in the second half of the normal menstrual cycle, and menstrual flow begins when the corpus luteum degenerates. (2) That progestin administration postpones natural menstruation and suppresses artificial menstruation produced by estrogen deprivation in castrate monkeys. (3) Progestin has been reported to counteract bleeding in certain conditions of uterine hyperplasia. *Dosage:* The administration of ½ to 1 international unit daily for a period of three to six days is recommended. Larger doses may be indicated.

Standardization.—The International Standard preparations of progesterone contain one unit of activity in 1.0 mg. Assay is based on progestational change induced in the uteri of immature or ovariectomized rabbits.

PREPARATIONS

Progesterone, *Progesteronum*, U.S.P. *Dosage:* Intramuscular, 5 mg. (1/12 grain).

Anhydrohydroxyprogesterone, *Anhydrohydroxyprogesteroni*, U.S.P. ($C_{21}H_{28}O_2$). *Dosage:* 10 mg. (1/6 grain), orally.

Anhydrohydroxyprogesterone Tablets, *Tabellae Anhydrohydroxyprogesteroni*, U.S.P. *Dosage:* 10 mg. (1/6 grain), usually available in 5 or 10 mg. tablets.

D. Male Sex Hormones

Androgens

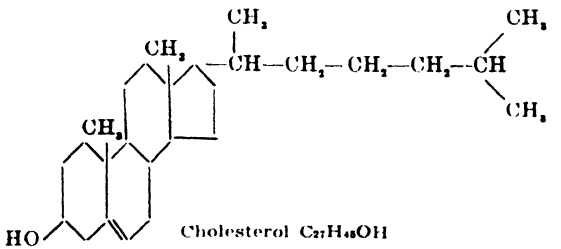
The normal development and maintenance of male sexual characters depends on an adequate supply of male sex hormone. Our early knowledge of the function of the male sex hormones was obtained from castration and transplantation studies. It is only within recent years that adequate preparations of the testicular hormone have become available.

In the mammalian organism both sexes elaborate male as well as female sex hormones. These two hormones are antagonistic, and hence it is possible to suppress effects induced by the female sex hormone by the administration of an excess of male hormone.

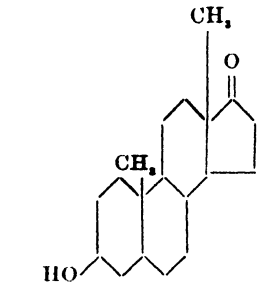
The procedure of Koch and his co-workers for the determination of androgenic activity which utilized the growth response of the capon's comb, provided the necessary tool which finally led to the isolation

of the male sex hormones or androgens. Butenandt (1931) is credited with the isolation of the male sex hormone, androsterone, from urine, but to Ruzicka and his co-workers (1934) belongs the credit for the chemical synthesis and the elucidation of the chemical nature of these compounds.

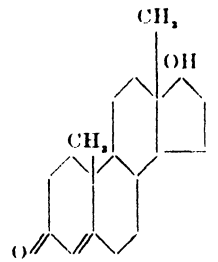
At present the androgens of interest include the urinary androgens —androsterone, dehydroandrosterone, and testosterone isolated from interstitial cells. Commercially testosterone is prepared synthetically, and is generally marketed in the form of testosterone propionate. Methyltestosterone has been advanced for oral therapy. The structural relationship between the androgens and cholesterol ($C_{27}H_{46}OH$) is shown. Inspection of the respective formulas clearly shows the close relationship between the male and female sex hormones.



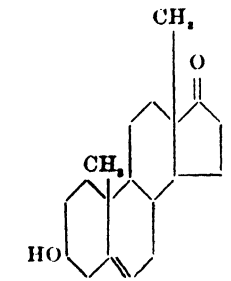
Cholesterol $C_{27}H_{45}OH$



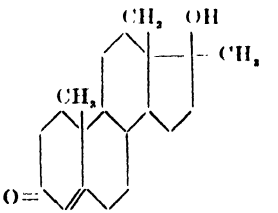
Androsterone $C_{19}H_{30}O_2$



Testosterone $C_{19}H_{28}O_2$



Dehydroandrosterone $C_{19}H_{28}O_2$



Methyltestosterone $C_{20}H_{30}O_2$

Testosterone.—Because of its relatively great androgenic activity, its presence in the testes, and its ability to duplicate the actions of the testes hormone, it is considered the true testicular internal secre-

tion. In all probability the urinary androgens are derived from testosterone by chemical changes in the body.

The testicular hormone, testosterone, is responsible for the development and maintenance of the accessory male organs and characteristics. Following castration in the male, seminal vesicles, penis, and prostate undergo atrophy. Sexual activity is depressed and libido is diminished. Testosterone administered by injection restores these structures and functions to normal.

Androgens inhibit the activity of the anterior pituitary and gonads. Spermatogenesis is retarded and may be completely depressed. The androgens may also exert certain metabolic effects similar to those produced by the adrenal cortex, i.e., virilism and sexual precociousness, trophic action on the skeletal musculature, and retention of essential cellular constituents.

The formation of spermatozoa in the testes is not ordinarily influenced by mechanical treatment, two types of agents are available which produce certain effects. When the formation of testosterone is impossible (eunuchism), direct stimulation is indicated. On the other hand, when formation is only deficient (cryptorchidism), testosterone is contraindicated because it may inhibit natural production of male hormone. Stimulation by the interstitial cell hormone from the placenta or pituitary may be effective. For this purpose chorionic gonadotropin is indicated.

Therapeutic Uses.—Androgens are used mainly for replacement therapy in castration and eunuchoidism. It also has been recommended for a variety of disorders in women, such as dysmenorrhea, functional uterine bleeding, and menopausal symptoms.

Eunuchism which results from castration is best treated by substitution therapy with testosterone. Treatment is started immediately with the patient if an adult, and at ten or twelve years if a child. Therapy is continued for life and allows him to continue or become a normal male. *Eunuchoidism* is a hypogonadism in which some ability to produce testosterone remains. This condition is often present in cryptorchism, in the adiposogenital syndrome, and following various infections of the testes. If deficiency is due to loss or damage to testicular tissue, treatment with testosterone is indicated; the stimulating effect of chorionic gonadotropin is probably of no value, but may be tried. Response may be satisfactory and the use of testosterone with its possible suppression of testicular action may be avoided. The use of gonadotropin first and then testosterone may be necessary for full response.

Testosterone may be given intramuscularly as testosterone in oil. A dose of 25 mg. three times weekly is believed to produce a maximum effect; later, reduction may be possible. Methyltestosterone is an effective oral preparation. The dose is 30 to 60 mg. daily. Pellets, for subcutaneous implantation and prolonged effect are available, and this type of administration is used where treatment is well established.

Androgens in the Female.—The usual action of male sex hormones in the female include the following: (1) inhibition of the gonadotropic activity and anterior pituitary; (2) suppression of ovarian follicle development, ovulation, corpus luteum formation, and inhibition of estrogen and progesterone secretion; (3) abolition of menstrual cycle; (4) abolition of normal endometrial changes and normal changes in vaginal mucosa; (5) prevention of estrogen withdrawal bleeding; and (6) induction of masculinization. On the basis of these actions,

androgen has been recommended for a variety of female disorders. The uses mentioned in the following paragraph are indicative of some of its advantages.

In the female, testosterone produces striking effects and is used in the treatment of certain gynecologic conditions. Since testosterone inhibits the gonadotropic action of the pituitary it has been used to treat menopausal symptoms. Its ability to suppress menstruation has been utilized in the treatment of dysmenorrhea and functional uterine bleeding. In *dysmenorrhea,* methyltestosterone, 1-2 tablets of 10 mg. per day orally may yield good results in a small number of cases; the parenteral administration of 10 to 25 mg. at weekly intervals is indicated. Seventy to 150 mg. per month will give good results in over half of the patients. Testosterone propionate has proved valuable in the alleviation of *congestion* and the *cessation* of *lactation.* The implantation of pellets of testosterone propionate is recommended for the alleviation of symptoms that usually attend *fibromyomas of the uterus* in those cases in which surgery is contraindicated. Small doses, 5 to 10 mg. administered on the fifteenth, twentieth, and twenty-fifth day of the menstrual cycle, have been found satisfactory in the treatment of *hypermenorrhea.* Larger doses (200 mg.) may be of value in stopping severe *menometrorrhagia.* Methyl testosterone, 10 to 20 mg. daily by mouth, has been recommended for treatment of frigidity in females (Smith, 1943).

Shute (1941) found testosterone propionate effective in the treatment of nausea and vomiting of early pregnancy.

Contraindications in the Female.—If symptoms of acne, enlarged clitoris, voice changes or hirsutism appear, discontinue testosterone therapy. It is safe to administer up to 200 mg. per month.

Administration.—*Testosterone propionate* is the form in which the male hormone is usually used clinically. It is supplied in sesame oil for intramuscular injection and as a 0.2 per cent ointment for percutaneous administration. In the treatment of hypogonadism the dose of testosterone varies from 5 to 25 mg. three times a week until the desired action is obtained. A maintenance dose of small size may then be given. Nightly administration of the 0.2 per cent ointment may be sufficiently effective to maintain the patient. About 4 grams of the ointment containing 8 mg. of testosterone per night are indicated. Pellets of testosterone propionate have been used for subcutaneous implantation. This procedure is effective and economical and obviates frequent injection.

Methyl testosterone has recently been prepared synthetically and is of interest because of its effectiveness when administered orally. This substance has been shown to be as effective orally as one-third to one-fourth the amount of injected testosterone propionate necessary for adequate replacement therapy in castrate animals. On the basis of available reports 50 to 100 mg. of this material daily are necessary for complete replacement therapy in the castrate. The reports regarding the use of this substance in menstrual conditions and prostatism are few and inconclusive, hence physicians should prescribe their usage with due consideration of the expense involved balanced against their possible benefit.

PREPARATIONS

Testosterone Propionate, *Testosteroni Propionas,* U.S.P. *Dosage:* Intramuscular, 25 mg. (5/12 grain), usually dissolved in oil for injection.

Methyltestosterone, *Methyltestosteronum*, U.S.P. $C_{20}H_{30}O_2$. *Dosage:* Oral, 10 mg. (⅙ grain); sublingual, 5 mg. (1/12 grain).

Methyltestosterone Tablets, *Tabellae Methyltestosteroni*, U.S.P. *Dosage:* Oral, 10 mg. (⅙ grain), sublingual, 5 mg. (1/12 grain), methyltestosterone, usually available in tablets containing these amounts.

PINEAL

The pineal gland is a small body situated underneath the posterior end of the corpus callosum. The structure of this gland suggests an endocrine function, but it is uncertain whether it is an organ of internal secretion. Some have reported precocious sexual, mental, and bodily development following tumors of the pineal. Most observations have been unconfirmed, so final judgment as to the rôle of the pineal gland must be reserved until more evidence is available.

THYMUS

The rôle of the thymus gland is not known. Numerous reports have associated it with growth, but evidence, on the whole, is not convincing. It is known, however, that the gland is proportionally larger at birth than at any other time, and that it continues to grow until puberty, after which it undergoes involution. Since thymic involution is delayed by castration, but is most pronounced at the age of puberty, several investigators believe that the gland is related in some way to sexual development. The suggestion has been made that the thymus is of importance as a factor in racial development.

HORMONES OF GASTROINTESTINAL TRACT

The hormones of the gastrointestinal tract are of great physiologic interest. They include *gastrin*, the hormone that regulates gastric secretion; *secretin*, associated with pancreatic secretion; *cholecystokinin* that activates the gall bladder; *enterogastrone* and *urogastrone*, the gastric inhibitory hormones; *enterocrinin* associated with intestinal secretions, but distinguished from vasodilator substances, secretin and enterogastrone; and *duodenin*, an islet-stimulating hormone. Both enterogastrone and urogastrone show great promise in the treatment of peptic ulcer (Bockus, 1948).

Space will not permit discussion of these most interesting and promising substances. Of interest, however, is the following statement by Ivy (1941): "Histamine, if it is gastrin, and secretin possess diagnostic value. Cholecystokinin is of potential diagnostic value. Enterogastrone and urogastrone possess therapeutic promise."

ANTIHORMONES

Long-continued injections of certain hormones give rise to a lowered response or even to complete lack of response on the part of the recipient to further injections. Collip (1934) explained the phenomenon by postulating the presence of antihormones which are considered to be antagonistic to the true hormones. More recent investigation indicates that the development of neutralizing substances is caused primarily by contaminating proteins rather than by the hormone itself. Since inactivated extracts still produce the reaction and, since daily implants of pituitary fail to induce the inhibitory effects obtained when

extracts are employed, it is believed by some that the antihormone-like action is due to contaminating substances. Furthermore, it should be pointed out that there are no known antibodies for the purified hormones, i.e., thyroxin, progesterone. Further knowledge of antihormones will be followed with great interest.

References

General

Bard, Philip: Macleod's Physiology in Medicine, St. Louis, 1938, The C. V. Mosby Co.

Beach, F. A.: Hormones and Behavior, New York, 1948, Paul B. Hoeber, Inc.

Cooke, W. R.: Essentials of Gynecology, Philadelphia, 1942, J. B. Lippincott Co.

Dodds, E. C.: Hormones and Their Chemical Relations, Lancet 1: 931, 987, 1048, 1934.

Glandular Physiology and Therapy: Special Articles, J. A. M. A., 1942.

Grollman, Arthur: Essentials of Endocrinology, Philadelphia, 1941, J. B. Lippincott Co.

New and Nonofficial Remedies: Chicago, 1947, American Medical Association.

Novak, Emil: Gynecology and Female Endocrinology, Boston, 1942, Little, Brown & Co.

Sevringhaus, E. L.: Endocrine Therapy in General Practice, Chicago, 1940, Year Book Publishers.

Smith, George Van S.: The Present Status of Hormone Therapy in Gynecology, M. Clin. North America 27: 1373, Sept., 1943.

Symposium on Endocrinology: Medical Clinics of North America, Philadelphia, January, 1949, W. B. Saunders Co.

The Hormones, Ann. Rev. Biochem., 1932-1941.

Thompson, W. O.: What's New in Endocrinology, J. A. M. A. 136: 314, 1948.

Turner, C. D.: General Endocrinology, Philadelphia, 1948, W. B. Saunders Co.

Werner, A. A.: Endocrinology, Philadelphia, 1942, Lea and Febiger.

Wolf, Wm.: Endocrinology in Practice, Philadelphia, 1937, W. B. Saunders Co.

Pituitary

Abel, J. J.: Physiological, Chemical and Clinical Studies on Pituitary Principles, Harvey Lectures 19: 154, 1923-1924.

Association for Research in Nervous and Mental Disease. The Pituitary Gland, Baltimore, 1938, The Williams and Wilkins Co.

Blotner, H.: Pitressin Tannate in Oil in the Treatment of Diabetes Insipidus, J. A. M. A. 119: 995, 1942.

Collip, J. B.: Some Recent Advances in the Physiology of the Anterior Pituitary, J. Mt. Sinai Hosp. 1: 28, 1934.

Cushing, Harvey: The Pituitary Body Hypothalamus, and Parasympathetic Nervous System, Springfield, Ill., 1932, Charles C Thomas.

Evans, H. M., Meyer, K., and Simpson, M. E.: The Growth and Gonad-Stimulating Hormones of the Anterior Hypophysis, Memoirs Univ. Calif., Vol. II, University of California Press, 1933.

Fevold, H. L., Lee, M., Hisaw, F. L., and Cohn, E. J.: Separation of Five Anterior Pituitary Hormones, Endocrinology 26: 999, 1940.

Geiling, E. M. K.: The Pituitary Body, Physiol. Rev. 6: 62, 1926.

Jones, G. M.: Diabetes Insipidus—Clinical Observations in Forty-two Cases, Arch. Int. Med. 74: 81, 1944.

Pickford, M.: Control of the Secretion of Antidiuretic Hormone From the Pars Nervosa of the Pituitary Gland, Physiol. Rev. 25: 573, 1945.

Russel, J. A.: The Relation of the Pituitary to Carbohydrate Metabolism, Physiol. Rev. 18: 1, 1938.

Van Dyke, H. B.: The Physiology and Pharmacology of the Pituitary Body, Vol. II, 1939, Univ. Chicago Press.

Thyroid

Chapman, E. M., and Evans, R. D.: The Treatment of Hyperthyroidism With Radioactive Iodine, J. A. M. A. 131: 86, 1946.

Crile, George: Diagnosis and Treatment of Diseases of the Thyroid Gland, Philadelphia, 1932, W. B. Saunders Co.

Harington, C. R.: The Thyroid Gland, London, 1933, Oxford University Press.

Marine, David: Glandular Physiology and Therapy, Chicago, 1935, American Medical Association.

McClendon, J. F.: Iodine and Incidence of Goiter, Minneapolis, 1939, University of Minnesota Press.

Means, J. H.: The Thyroid and Its Diseases, ed. 2, Philadelphia, 1948, J. B. Lippincott Co.

Soskin, S., and Levine, R.: Recent Advances in Physiology of the Thyroid and Their Clinical Application, Arch. Int. Med. 74: 375, 1944.

Thompson, W. O., Thompson, P. K., Taylor, S. G., Nadler, S. B., and Dickie, L. F. N.: Pharmacology of Thyroid in Man, J. A. M. A. 104: 481-502, 1935.

Williams, R. H.: Thiouracil Treatment of Thyrotoxicosis. I. The Results of Prolonged Treatment, J. Clin. Endocrinol. 6: 1, 1946.

Williams, R. H., Clute, H. M., Anglem, T. J., and Kenney, F. R.: Thiouracil Treatment of Thyrotoxicosis. II. Toxic Reactions, J. Clin. Endocrinol. 6: 23, 1946.

Parathyroid

Albright, Fuller: The Parathyroids—Physiology and Therapeutics, J. A. M. A. 117: 527, Aug. 16, 1941.

Aub, J. C.: Parathyroid Hormone Therapy; Glandular Physiology and Therapy, Chicago, 1935, American Medical Association.

Hanson, A. M.: The Hormone of the Parathyroid Gland, Proc. Soc. Exper. Biol. & Med. 22: 560, 1925.

MacBryde, Cyril: The Treatment of Parathyroid Tetany With Dihydrotachysterol, J. A. M. A. 111: 304, 1938.

Rose, E.: Hypoparathyroidism, Clinics 1: 1179, 1943.

Sevringhaus, E. L.: Activated Sterols and Calcium Salts in the Treatment of Parathyroid Tetany, Am. J. M. Sc. 203: 726, 1942.

Shelling, D. H.: The Parathyroids in Health and Disease, St. Louis, 1935, The C. V. Mosby Co.

Thomson, D. L., and Collip, J. B.: The Parathyroid Glands, Physiol. Rev. 12: 309, 1932.

Pancreas

Aldersberg, D., and Dolger, H.: Insulin Mixtures in the Treatment of Diabetes: Variable Versus Fixed Ratios of Insulin and Protamine Zinc Insulin, J. A. M. A. **128**: 414, 1945.

Bailey, O. T., Bailey, C. C., and Hagan, W. H.: Alloxan Diabetes in the Rabbit: A Consideration of Morphologic and Physiologic Changes, Am. J. M. Sc. **208**: 450, 1944.

Banting, F. G., and Best, C. H.: The Internal Secretion of the Pancreas, J. Lab. & Clin. Med. **7**: 251-266, 1922.

Brunschwig, A., Allen, J. G., Owens, F. M., and Thornton, T. F.: Alloxan in the Treatment of Insulin-Producing Islet-cell Carcinoma of Pancreas, J. A. M. A. **124**: 212, 1944.

Cori, C. F., and Cori, G. T.: Carbohydrate Metabolism, Ann. Rev. Biochem. **2**: 129, 1933; Ibid. **3**: 151, 1934; Ibid. **4**: 183, 1935.

del Fierro, R. S., and Sevringhaus, E. L.: Clinical Use of New Types of Modified Protamine Zinc Insulin, Ann. Int. Med. **22**: 667, 1945.

Dragstedt, L. R.: The Present Status of Lipocaic, J. A. M. A. **114**: 29-32, Jan. 6, 1940.

Hagedorn, H. C., Norman Jensen, B., Krarup, N. B., and Wodstrup, I.: Protamine Insulinate, J. A. M. A. **106**: 177-180, 1936.

Jensen, H. F.: Insulin: Its Chemistry and Physiology, London, 1938, Oxford University Press.

Joslin, E. P.: A Diabetic Manual, ed. 6, Philadelphia, 1937, Lea and Febiger.

Mering, J. von, and Minkowski, O.: Diabetes Mellitus nach Pankreas Extirpation, Centralbl. f. Klin. Med. **10**: 393, 1889.

Scott, D. A., and Fischer, A. M.: Studies on Insulin and Protamine, J. Pharmacol. & Exper. Therap. **58**: 78-92, 1936.

Soskin, S., and Levine, R.: Carbohydrate Metabolism, ed. 3, Chicago, 1948, University of Chicago Press.

Wilder, R. M.: Therapy and Preparations of Pancreas, J. A. M. A. **117**: 930-932, Sept. 13, 1941.

Adrenals

Addison, T.: On the Constitutional and Local Effects of Disease of the Suprarenal Capsules, London, 1855.

Britton, S. W.: Adrenal Insufficiency and Related Considerations, Physiol. Rev. **10**: 617, 1930.

Cannon, W. B., and Rosenblueth, A.: Autonomic Neuro-Effector Systems, New York, 1937, The Macmillan Co.

Goldzieher, M. A.: The Adrenal Glands in Health and Disease, Philadelphia, 1945, F. A. Davis Co.

Grollman, A.: The Adrenals, Baltimore, 1936, Williams & Wilkins Co.

Kendall, E. C.: The Functions of the Adrenal Cortex, Proc. Staff Meet., Mayo Clin. **13**: 519-523, 1938.

Reichstein, T., and Shoppee, C. W.: The Hormones of the Adrenal Cortex, Vitamins & Hormones **1**: 345, 1945.

Swingle, W. W., and Pfiffner, J. J.: The Adrenal Cortical Hormone, Medicine **11**: 371, 1932.

Thorn, G. W., and Firor, W. M.: Desoxycorticosterone Acetate Therapy in Addison's Disease, J. A. M. A. **114**: 2517-2525, 1940.

Thorn, G. W.: Clinical Use of Extracts From Adrenal Cortex and of Synthetic Products Having Similar Actions, J. A. M. A. **125**: 10, 1944.

Williams, R. H., Whittenberger, J. L. Bissell, G. W., and Weinglass, A. R.: Treatment of Adrenal Insufficiency, J. Clin. Endocrinol. **5**: 163, 1945.

Sex Hormones

Allen, E., Danforth, C. H., and Doisy, E. A.: Sex and Internal Secretions, ed. 2, Baltimore, 1939, Williams & Wilkins Co.

Bishop, P. M. F., Boycott, M., Kelles, R., MacGregor, T. N., and Murless, B. C.: Estrogenic Properties of Stilbestrol Dipropionate and Hexestrol, Lancet **1**: 629-633, April 6, 1940.

Burrows, H.: Biological Actions of Sex Hormones, Chicago, 1945, Cambridge University Press.

Campbell, R. E., and Sevringhaus, E. L.: Pituitary Gonadotropic Extracts for Treatment of Amenorrhea, Menorrhagia and Sterility, Am. J. Obst. & Gynec. **37**: 913, 1939.

Council Report: The Present Status of Therapy With Chorionic Gonadotropin, J. A. M. A. **114**: 487-489, 1940.

Davis, M. E.: Clinical Study of Stilbestrol, Am. J. Obst. & Gynec. **39**: 938, 1940.

Dodds, E. C.: Hormones in Cancer, Vitamins & Hormones **2**: 353, 1944.

Dodds, E. C.: Possibilities in the Realm of Synthetic Estrogens, Vitamins & Hormones **3**: 229, 1945.

Evans, H. M., Meyer, K., and Simpson, M. E.: The Growth and Gonad-Stimulating Hormones of the Anterior Hypophysis, Memoirs University of California, Vol. II, University of California Press, 1933.

Fluhmann, C. F.: Clinical Use of Extracts From the Ovaries and of Synthetic Products Having Similar Actions, J. A. M. A. **125**: 1, 1944.

Freed, S. C.: The Treatment of Pre-menstrual Distress With Special Consideration of the Androgens, J. A. M. A. **127**: 377, 1945.

Goldzieher, M. A.: Treatment of Menstrual Disorders With Prolactin, J. Clin. Endocrinol. **5**: 132, 1945.

Hamblen, E. C., and Davis, C. D.: Treatment of Hypo-ovarianism by the Sequential and Cyclic Administration of Equine and Chorionic Gonadotropins—So-called One-Two Cyclic Gonadotropic Therapy—Summary of 5 Years' Results, Am. J. Obst. & Gynec. **50**: 137, 1945.

Heckel, N. J.: Evaluation of Sex Hormones in the Treatment of Benign Prostatic Hypertrophy, Carcinoma of the Prostate and Other Diseases of the Genito-Urinary System, J. Clin. Endocrinol. **41**: 166, 1944.

Hufford, A. R.: The Synthetic Estrogen Octofollin (in Oil), J. A. M. A. **123**: 259, October, 1943.

Koch, F. C.: The Chemistry and Biology of Male Sex Hormones, Physiol. Rev. **17**: 153, 1937.

MacBryde, C. M., et al.: The Synthetic Estrogen Diethylstilbestrol, J. A. M. A. **117**: 1240, October, 1941.

Mazer, Charles: Endocrine Treatment in General Practice, J. Indiana M. A. **34**: 584, November, 1941.

McKenzie, C. H.: Diethylstilbestrol (101 References), Journal-Lancet **61**: 94-100, March, 1941.

Morgan, T. N.: The Male Sex Hormones, Practitioner **154**: 149, 1944.

Papanicolaou, G. N., and Shorr, E.: Action of Ovarian Follicular Hormone on the Menopause as Indicated by Vaginal Smears, Am. J. Obst. & Gynec. **31**: 806-831, May, 1936.

Roberts, H. K., Loeffel, E., and MacBryde, C. M.: Octofillin, a New Synthetic Estrogen, J. A. M. A. **123**: 261, October, 1943.

Stoddard, F. J.: The Abuse of Endocrine Therapy in Gynecology, J. A. M. A. **129**: 508, 1945.

Thompson, W. O.: Uses and Abuses of the Male Sex Hormone, J. A. M. A. **132**: 185, 1946.

Zondek, B., and Sulman, F.: The Mechanism of Action and Metabolism of Gonadotropic Hormones in the Organism, Vitamins & Hormones **3**: 297, 1945.

Thymus and Pineal

Anderson, D. H.: The Relationship Between the Thymus and Reproduction, Physiol. Rev. **12**: 1, 1932.

Blalock, A., Harvey, A. M., Ford, F. R., and Lilienthal, J. L., Jr.: The Treatment of Myasthenia Gravis by Removal of the Thymus Gland, Preliminary Report, J. A. M. A. **117**: 1529, 1941.

Gladstone, R. J., and Wakeley, C. P. G.: The Pineal Gland, Baltimore, 1940, Williams and Wilkins Co.

Nelson, O.: Relation of the Thymus and Pineal Glands to Genital Function, in Allen: Sex and Internal Secretion, Baltimore, 1939, Williams and Wilkins Co.

Gastrointestinal Tract

Ivy, A. C.: Internal Secretions of the Gastrointestinal Tract (60 references), J. A. M. A. **117**: 1013-1017, Sept. 20, 1941.

Antihormones

Collip, J. B.: Antihormones, A. Research Nerv. & Ment. Dis. **17**: 268, 1938.

Thompson, K. W.: Antihormones, Physiol. Rev. **21**: 588, 1941.

CHAPTER XXIII

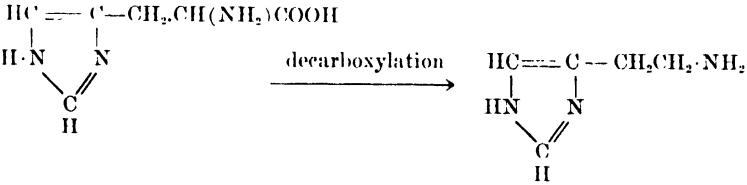
MISCELLANEOUS DRUGS

HISTAMINE AND ANTIHISTAMINE DRUGS

Since histamine has been shown to have an important, though partial, role in allergenic relations, much interest and effort has been made to develop compounds that oppose it. Search for suitable histamine-antagonizing agents has resulted in the development of several relatively nontoxic compounds useful in the symptomatic treatment of certain allergenic phenomena. These compounds must, however, be regarded as adjuncts to treatment, and do not replace fundamental specific methods known to be useful in the treatment of allergenic conditions. The antihistamine drugs are recent additions to therapeutics. It is believed that future investigations may open fields of usefulness for this group of drugs. Indiscriminate use may be fraught with toxic reactions and should be discouraged.

Histamine

Histamine, beta-iminazolylethylamine, a normal constituent of the body, is a derivative of amino acid histidine. In 1910 Ackerman prepared synthetic histamine by the action of putrefactive organisms on the amino acid histidine.



Histidine Histamine

Pharmacological Action. The histamine formed in the digestive tract by bacteria is probably not absorbed. When histamine is administered orally, it is also destroyed and has little effect; but when injected subcutaneously or intravenously, it produces intense direct stimulation of smooth muscle, including those of the bronchi, intestines, and arteries. The arteries and capillaries are dilated and blood pressure falls. The salivary, gastric, and pancreatic glands are stimulated.

In the stomach histamine stimulates the motility and production of gastric juice, in cases of achlorhydria, a common clinical test is to inject subcutaneously a histamine salt (0.5 mg.). If no gastric acid is produced within an hour, probably complete achylia gastrica is present. It is sometimes necessary to do repeated tests to elicit acid secretion in refractory cases.

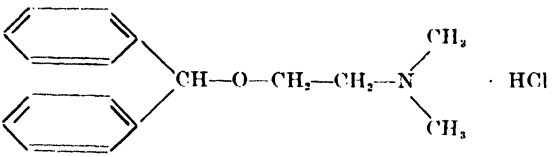
Toxic reactions may follow histamine injection, including generalized urticaria, severe dyspnea from bronchial spasm, and severe vasomotor reactions. The antidote is epinephrine; 1 mg. in the blood will neutralize the effect of 10 mg. of histamine. Ephedrine and aminophylline are effective antidotes for bronchial spasm. Since reactions may follow the use of 1 mg. in testing gastric function, 0.5 mg. is recommended. Besides being employed as a test for gastric function, his-

tamine has been employed in small increasing dosage as a desensitizer in recurrent allergies. It has been recommended in various other conditions including neurovascular headache, vasomotor rhinitis, neuritis, rheumatic affections, multiple sclerosis (Mayo Clinic), and related conditions. Results have not been by any means encouraging.

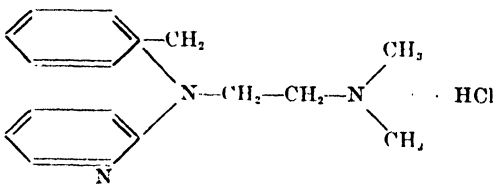
Histaminase, an enzyme capable of destroying histamine in vitro, appears to have little effect in vivo, although once widely recommended for the treatment of allergenic disorders. It fails to modify histamine shock and also anaphylactic shock. A number of favorable reports, however, appear in regard to the use of histamine. Claims for the effectiveness of histaminase in physical allergies, however, appear to be unsupported by accepted evidence. Intravenous and intramuscular administration of histamine apparently has no effect on the histamine present in the body. There is no physiological basis for its use, and there is no indication that it is useful in therapy.

Antihistamine Drugs

The actions of histamine may be antagonized by a variety of substances including benadryl, pyribenzamine, antergan and neoantergan.



Benadryl
(Diphenhydramine Hydrochloride)



Pyribenzamine
(Tripelennamine Hydrochloride)

Benadryl is one of the most important antihistamine substances (W. A. Selle, 1946). Its most important actions are: (1) it has the ability to alleviate bronchial constriction and asthma of histamine or anaphylactic shock; (2) it relieves the vasodepressor effects of histamine; (3) it relaxes smooth muscle. It antagonizes the spasmogenic effects of barium and acetylcholine on the guinea-pig intestine.

Toxic reactions may follow benadryl administration. Full dosage may cause drowsiness which may be overcome by caffeine, amphetamine, or ephedrine. Nausea, dizziness, nervousness, muscle twitching, disorientation, hysterical reactions, and collapse have been reported.

Benadryl promises to be of therapeutic value in the treatment of urticaria, angioneurotic edema, allergic rhinitis, and drug allergies.

Encouraging results have been reported following its use in contact dermatitis. The use of benadryl in the prevention of transfusion reactions suggests that the drug may be efficacious in this condition (Blumenthal and Rosenberg, 1947).

The drug is usually administered by mouth in doses of 25 to 100 mg. three or four times a day. Intramuscularly, it may be given in a solution, 10 mg. in 1 cc. Intravenously it may be administered by continuous drip or by injection of physiological saline containing 50 to 60 mg. in 100 cc.

Pyribenzamine is another chemical substance with strong antihistamine properties. Its pharmacologic and toxicologic reactions resemble those of benadryl. It is reported to produce less nausea and drowsiness. It is believed to be more effective than benadryl in both seasonal and nonseasonal allergic rhinitis.

Antergan and Neo-Antergan

Halpern (1942) prepared a series of ethylenediamine compounds; of these, dimethylaminoethylbenzylanilin (antergan) showed promising results in various allergic disorders. Later, Bovet and his co-workers discovered another ethylenediamine derivative, N',N'-dimethyl-N-α-pyridylethylene-diamine (neo-antergan), which shows great promise in allergic conditions and is reported to be better tolerated than antergan. Both antergan and neo-antergan have had little clinical trial in America.

Still more recently, Halpern of France reported on a new series of compounds, the thiodiphenylamine derivatives, which were more effective and less toxic in animal experiments than any previously reported.

Efficiency of Antihistamine Drugs

Clinically the antihistamine drugs exhibit a powerful antagonism to histamine. Two actions are outstanding—they dry up mucous secretion and inhibit whealing. Symptoms of urticaria respond dramatically in about 85 to 95 per cent of the patients within twenty minutes (see Table XXXII) following 50 to 100 mg. of the drug. The action is palliative and symptoms recur after four to six hours. In hay fever the antihistamine drugs are beneficial during the early part of the season when there is no evidence of secondary infection. In asthma, when the disease has progressed to the stage characterized by thick tenacious expectoration, benefit from oral administration may not be evidenced. If the drug is given intravenously, severe attacks respond temporarily when

Table XXXII

Estimated Efficacy of the Antihistaminic Drugs

	Per cent of efficacy*
Urticaria	85 to 95
Hay fever	70 to 80
Vasomotor rhinitis	60 to 70
Asthma: Oral	40 to 50
Intravenous	65 to 75
Pruritus of eczema and contact dermatitis	30 to 40
Migraine	25 to 35
Gastrointestinal allergy	Doubtful

*Based on data of Dr. Carl Arbesman, Buffalo, and the review of Dr. S. M. Feinberg.

other drugs have failed. In allergic shock, antihistamine drugs in doses of 10 to 50 mg. are indicated.

Contact dermatitis and pruritus of allergic eczema are controlled by antihistamine drugs. The anesthetic properties of these agents may be utilized by topical application in ointments and compresses. In gastrointestinal allergy reports indicate that these drugs may be useful in some instances.

Toxic manifestations such as dizziness, drowsiness, and headaches may occur in 20 to 25 per cent of patients taking antihistamine drugs. These reactions occur more frequently with benadryl than with pyribenzamine and neoantergan. Prolonged use (months) has not thus far resulted in any demonstrable organic damage. Cumulative action or addiction has not been reported.

PROTEIN AND AMINO ACID PREPARATIONS

Protein and amino acid preparations may be divided into two general classes: (1) mixtures of amino acids essential to human nutrition; (2) individual amino acids that are indicated for specific therapeutic purposes.

Preparations of the first class include various protein hydrolysates, and mixtures of synthetic amino acids. Protein hydrolysates are artificial digests of protein derived by acid, enzymatic, or other hydrolysis of casein, lactalbumin, or any other suitable protein.

Normally there are large reserves of protein and amino acids in the liver, muscle, and other tissues. These reserves, however, may be depleted by (1) inadequate protein intake, (2) faulty digestion and absorption, (3) increased demand, e.g., rapid growth, pregnancy and lactation, (4) increased protein loss, e.g., albuminuria, fever, hemorrhage, surgery, etc., or (5) impaired protein synthesis, e.g., liver disease.

The amino acids that are now regarded as indispensable for protein synthesis in the human being comprise those which the body cannot synthesize and are listed as follows: phenylalanine, tryptophane, methionine, lysine, leucine, isoleucine, threonine, valine, histidine, and arginine. The ten amino acids are usually found in mixtures indicated for protein replacement. There is some question about the indispensability of histidine and arginine in adult man. A mixture of amino acids, combined as in the protein concentrates, never has a biological value equal to that of the protein itself (Murlin, 1945). Their deficiency, however, causes hypoproteinemia, which is due to a lowered osmotic pressure of the blood, and is the principal cause of edema. Madden, et al. (1946), reported that amino acids are not as well utilized parenterally as orally, and are less well utilized than natural foods.

Action and Uses.—Clinically, protein hydrolysates are useful for maintenance of positive nitrogen balance in conditions in which there is interference with ingestion, digestion, or absorption of food. These conditions are most frequently encountered in severe illness and after surgical operations involving the alimentary tract. Protein hydrolysates should not be employed as a substitute for food proteins if the latter can be adequately utilized. It is debatable whether hydrolysates are indicated in brief severe illnesses.

Protein hydrolysates are administered both orally and intravenously. *Intravenous injection* is contraindicated in severe hepatic insufficiency and in acidosis until the latter conditions is corrected. Injections may produce toxic effects such as nausea, vomiting, hyperpyrexia, vasodilata-

tion, abdominal pain, edema at site of injection, phlebitis, and thrombosis. Most reactions are traced to too rapid administration and lack of clean equipment.

The intravenous preparations are for emergencies. Amounts sufficient to provide 1.0 Gm. of amino acids per kilogram of body weight per day, or more, may be administered with 5 per cent dextrose, saline, or Ringer's solution, or distilled water to make a final volume of 500 cc. The rate of injection must be slow. A solution may be administered intravenously at a rate not to exceed 15 Gm. of amino acid per hour. In some conditions a slower rate is desirable.

Clinical experience indicates that parenteral injections of amino acids are an important nutritional advance but impractical when used as the only source of nitrogen over long periods of time (Hoffman, 1947).

Oral administration of protein hydrolysates are indicated (1) in diets of infants allergic to milk, when the allergy cannot be met by other foods; (2) in the treatment of peptic ulcer and in ulcerative colitis; and (3) in supplementing high protein intake when ordinary foods are inadequate to accomplish the purpose. Oral preparations are quite distasteful and are used flavored or given with vegetable juices. Fruit juices are usable but unsatisfactory.

Dosage: There is as yet insufficient information available to give the exact dosage estimates for the amino acids. Probably the daily requirements for the individual requiring amino acids ranges from 0.3 to 5 Gm. each, per day. There are wide variations in individual requirements, but it is estimated that the amino acid requirement will ordinarily be met by a diet containing 70 Gm. of protein.

SNAKE VENOMS

Snake venoms have been put to a number of empirical uses for some time. Snake venom has been used for the following purposes: (1) to prepare antivenin, (2) for the treatment of hemorrhagic conditions, (3) for the relief of pain, and (4) to a lesser extent for the control of discomfort in tabetic crises, in angina pectoris, and in the Parkinson syndrome.

General Discussion.—The actual composition of snake venom is not altogether known. Dr. Adolph Monaelesser defines it admirably as follows: "Snake venom is composed of a mixture, in variable proportions, of protein substance, mucus and debris of epithelial cells, some fatty matter, and salts such as calcium chloride and phosphate, also ammonia and magnesia. The density is somewhat greater than that of water, varying in specific gravity from 1.030 to 1.050. The proteins contain the various active toxins, which by certain methods can be removed or some of them inactivated, as has been demonstrated by research in the New York Zoological Park."

Generally speaking, the venoms of all snakes are composed of two primary elements, a *hematoxin* and a *neurotoxin*. The former creates great destruction of the red blood cells and tissues, accompanied by swelling, discoloration and other manifestations. The neurotoxin produces little swelling, but its action is quite pronounced. It attacks the nerve centers, particularly of the sympathetic system, also the phrenic nerve. It may cause paralysis of the thoracic muscles to the extent of stopping respiration. The two types of toxins are separable and each can act without the other. Most venoms contain both toxins but in different ratios.

An example of the varying proportion of hematoxic and neurotoxic elements is well shown by the viper and the Indian cobra. They represent two extremes. The *symptoms* following the viper's bite are rapid and dangerous. Swelling and discoloration take place immediately. There is oozing of blood from the mouth and conjunctiva and even from the stomach. There are bloodlike ejections from the bladder. Coma and death may follow in six to twelve hours. On the other hand, the bite of the cobra causes slow and moderate swelling and little discoloration. Difficulty in breathing is an initial symptom which steadily increases.

The North American rattlesnakes, the copperhead, and the moccasin produce largely a hemolytic reaction, a reaction not as severe as that of the Central and South American vipers.

Pharmacology of Venom.—Various explanations for the action of venoms have been offered:

1. ANALGESIC ACTION caused by neurotoxin acting on the subcortical centers in the cerebrum. *Cobra toxin* was found (a) to be antagonistic to cerebral convulsions, (b) it influences the temperature-regulating center of the brain, (c) it increases mental activity and intelligence in nontoxic doses, and (d) it has a threshold of pain comparable to the effect of opium alkaloids. Furthermore, neurotoxin was found to be slow in establishing itself upon the nerve tissues; once fixed to the cell, however, its effects are long lasting. Thus, it is conceivable that these actions all tend to suppress the sensory impulse—pain.

2. LECITHINASE.—This enzyme changes lecithin to lysolecithin and may be a factor in altering nerve conductivity as nerve tissues are abundant in lecithin.

3. CHOLINESTERASE ACTION.—The curari-like effect of neurotoxin on the motor end plates of the muscles points to acetylcholine as a chemical transmitter of certain sympathetic effects. Actually, acetylcholine, present in excess in the tissues and produced by overstimulation of nerves, can be neutralized by venom which contains appreciable amounts of esterase. Thus the plasma esterase is increased and the transmission at the synapse from tissues to nerves, and vice versa, is prevented.

4. HISTAMINE.—It has been demonstrated that histamine is liberated by Australian snake venoms of the hemotoxic type; this is an important manifestation of the cytolytic activity of venoms. Histamine output varies with different venoms.

5. ADRENALIN.—Snake venoms have the ability of liberating adrenalin from the adrenal glands. The adrenalin-like effect of snake venoms, their antagonism to insulin and relief of hypoglycemic convulsions may play a role in the pharmacological action of venom.

Therapeutic Uses.—*Treatment of Snake Venom Poisoning.*—The first steps are ligation and incision of the wound. Then administer 10 cc. of polyvalent serum subcutaneously or, in cases in which symptoms develop rapidly, it may be given by vein. Repeat dosage if necessary. *Note: The Antivenin Institute of America* produces a polyvalent serum for bites of the rattlesnake, moccasin, and copperhead. The venom of these three types, largely of a hemotoxic nature, renders a serum of great therapeutic value.

Hemorrhagic Conditions.—Snake venom has only recently been recognized as a rational therapeutic agent in hemorrhagic conditions. The venom of Russell's viper, the tiger snake, in high dilutions, will coagulate blood *in vitro* and may be used in local bleeding. These venoms have relatively high coagulating powers in extreme dilutions (1:10,000 to 1:100,000 or more) and are useful in external bleeding which may occur in hemophiliacs following operative procedure.

Moccasin venom seems to be efficacious in the functional type of hemorrhage, i.e., *recurrent epistaxis, essential hematuria, and functional menorrhagia.*

As an Analgesic.—Cobra venom relieves pain through its action in the highest centers of the brain (Macht, 1936). It induces analgesia slowly (several days) but its action is much longer acting than that of morphine.

Angina Pectoris.—Intravenous injections of cobra venom every third day, beginning with 0.25 cc., followed by 0.50 cc., 0.75 cc., and 1 cc. have been used with some success (Bulbrich, 1937). *Parkinsonian Syndrome.*—Gayle and Williams, 1938, obtained good results in two-thirds of the patients treated. They administered cobra venom, 0.5 cc. the first day and 1 cc. every other day for ten doses. In *tabes dorsalis* excellent results were reported by Rottman (1937). Steinbrocker et al. (1940) reported promising results with cobra venom in the treatment of *arthralgias* and related conditions.

RHUS PREPARATIONS

Rhus preparations are used for the prevention and treatment of dermatitis resulting from contact with poison ivy, poison oak, and sumach. *Rhus toxicodendron, Rhus diversiloba,* and *Rhus venenata* are commonly known as poison ivy, poison oak, and poison sumac. The first two are probably identical, but poison sumac is a distinct species. The sap of all three contain a toxic substance called urushiol (a dihydroxybenzene with an aliphatic side chain of varying degrees of saturation) which will sensitize most people who come in contact with the broken leaves or twigs.

The majority of sensitive persons can be rendered resistant temporarily to contact with ivy by large doses of antigen administered orally. Large doses, however, may be dangerous and the immunity is brief. Evidence is available which indicates that the subcutaneous injection of several doses of extract of increasing strength renders many susceptible persons immune to contact. The later method probably is to be preferred.

Washing the parts of the body which come in contact with the plant with soap and water or with alcohol followed by soap and water removes much of the toxic resin and may prevent dermatitis.

PREPARATIONS

Poison Ivy Extract, N.N.R.—A solution of resin extracted from the fresh leaves of *Rhus toxicodendron.* For prevention of symptoms of dermatitis produced by contact with *Rhus toxicodendron. Dosage:* For prophylaxis, two injections of 1.0 cc. each may be given two weeks apart.

Poison Oak Extract, N.N.R.—A solution of resin extracted from the fresh leaves of *Rhus diversiloba.* Used for the prevention of symptoms of dermatitis produced from contact with *Rhus diversiloba. Dosage:* For prophylaxis, two injections of 1 cc. each, separated by an interval of two weeks.

Poison Sumac Extract, N.N.R.—A solution of a resin extracted from fresh leaves of *Rhus venenata* used for the prevention of dermatitis produced by contact with *Rhus venenata. Dosage:* Two injections of 1 cc. each, separated by an interval of two weeks.

ARSENIC

Arsenic has been known as a therapeutic agent for centuries. Although organic arsenical compounds are of major importance in the treatment of syphilis and certain protozoan diseases, other uses of arsenic in present-day therapeutics are very limited.

Arsenic is used therapeutically in the trivalent and pentavalent forms. The trivalent form produces typical arsenic reactions. These effects may be induced by the pentavalent form by reduction in the body to the trivalent form.

Metallic arsenic is insoluble and nontoxic. When taken by mouth, it is inactive, but the compounds which go into solution are all protoplasm poisons.

Pharmacological Action.—Inorganic arsenic possesses alterative, tonic and escharotic actions. The general actions of arsenic are due to the AsO_3 ion, and not to the element.

Absorption and Excretion.—Inorganic arsenic is rapidly absorbed into the system by any route of administration. It is even absorbed sufficiently from the skin to cause poisoning. When injected into the blood stream it is found to disappear rapidly and become deposited in the tissues. About 20 per cent is slowly eliminated in the feces and urine, the rest is stored in the tissues for some time and slowly lost through the hair and epidermis. Arsenic may be found in the skin and hair for months after it has disappeared from the urine and feces.

Mode of Action.—The action of arsenic may be due to either the oxygen combination, occurring as an ion, or to the arsenic ion (As^{+++}); since, however, As_2O_3 in alkalies ionizes as follows:

$$As_2O_3 + 6OH^- \rightarrow 3H_2O + 2AsO_3^{---}$$
$$As_2O_3 + 3CO_3^- \rightarrow 3CO_2 + 2AsO_3^{---}$$

it seems probable that the oxygen compound is the active agent.

Local Action.—The arsenicals are not precipitant and they therefore cause little irritation of the skin and mucous membranes, but if left in contact with the skin for some time, they produce a local hyperemia and even a vesicular pustular eruption. Arsenic is more active when applied to denuded surfaces, as it penetrates to some depth and causes acute pain. It is more destructive to pathologic cells, as evidenced by the fact that cancerous tissue may be destroyed without injury to the normal tissue. Since the deep cancerous tissue escapes, it is of no value for treatment of cancer. Arsenic causes local injury by first injuring the capillaries which subsequently leads to the death of the tissues.

Workers in arsenic may show local skin effects characterized by proliferation of the epithelium and, in the more severe cases, atrophy and degeneration.

Action on the Skin.—Arsenic produces a beneficial effect on the skin; the subcutaneous fat is increased and the complexion is improved. The coats of domestic animals, e.g., the horse, are rendered thicker and more glossy. The action may be due to an increased blood supply furnished to the skin by local vasodilation.

Large doses in man may cause exfoliative dermatitis, keratosis, and a pigmentation or melanosis. This pigmentation may be due to increased destruction of the red corpuscles followed by subsequent deposition of hemoglobin derivatives.

Action on the Alimentary Canal.—Therapeutic doses of arsenic, administered orally or by injection, tend to increase the appetite and promote digestion. This action is explained by the specific action on the epithelium leading to increased secretion. Large doses cause a

gastroenteritis and a degeneration of epithelial tissue. The gastroenteritis produced differs from that caused by true corrosives in being accompanied by a profuse, serous diarrhea, owing to the greatly increased permeability of the dilated and paralyzed capillaries. There may also occur a fatty infiltration of the epithelial coat resembling a false membrane, or there may be only a cloudy swelling and fatty infiltration of the gland cells. The action is thought to be due to the extreme dilation of the intestinal vessels which gives rise to an appearance of swelling and congestion, which in turn causes edema and destruction of the epithelium.

Action on Metabolism.—The action of arsenic on metabolism resembles that of phosphorus. Therapeutic doses check oxidation and favor nutrition and growth. The bones grow larger and stronger and the nutrition of the skin and subcutaneous tissue is improved. Some investigators have observed no change in the growth of animals under prolonged arsenic treatment other than the production of bone with a greater density. Sollmann (1921) found that small doses of arsenic lessened the appetite and retarded the growth of rats. In poisoning by arsenic, distinct metabolic changes occur. Nitrogenous metabolism is increased, and the amount of nitrogen passed in the urine is also increased.

If the administration of arsenic is forced, severe anemia may follow, with ultimate degeneration of bone marrow.

Blood.—In certain forms of anemia, such as progressive pernicious and posthemorrhagic anemias, arsenic tends to stimulate the formation of red blood corpuscles. The improvement in anemias under arsenic has been suggested by Hill as being due to some ability of the arsenic to increase the resistance of the erythrocytes to dissolution. Others have attributed the effect to some unknown action on the bone marrow.

Action on Nervous System.—Small doses of arsenic, repeatedly given, seem to stimulate the nervous system in an unknown manner. Chronic poisoning (continuous stimulation) results in inflammation of the peripheral nerve tissues,-i.e., neuritis. Large doses of arsenic produce little inflammation but do cause paralysis of the nervous system and, through involvement of the medulla, produce death by respiratory failure.

Action on the Respiration.—Small doses of arsenic, administered orally, have little effect on respiration; injected intravenously, arsenic tends to increase the respiratory rate. Lethal doses arrest respiration before cardiac arrest occurs.

Action on Circulation.—The mammalian heart is little affected by arsenic; but a marked fall in blood pressure follows the injection of large doses intravenously. The fall in blood pressure is due to dilatation of the capillaries caused by direct action on their walls. The vessels of the splanchnic area seem most affected, leading to marked congestion of the stomach and bowel. Contributing effects to the fall in blood pressure are a somewhat weakened heart and a slight depression of the medullary centers.

Toxicology.—Poisoning by arsenic is usually for homicidal purposes. Arsenic trioxide, which lacks a distinctive taste, is often used. Suicidal cases may occur, and are usually the result of ingesting rat poison or Paris green. Accidental poisoning may occur due to the widespread use of arsenic compounds in medicine, and in the home. Arsenic poisoning in the industries is not very frequent in this country.

ACUTE ARSENIC POISONING.—Acute poisoning may follow the ingestion of white arsenic (arsenic trioxide), of Paris green (copper aceto-

arsenite) and of "rough on rats" (arsenous oxide and barium carbonate). These give rise to most of the accidental, homicidal, and suicidal cases of acute poisonings.

The first symptoms of poisoning are those of a violent irritant of the gastrointestinal tract, followed by vomiting, diarrhea, and burning pain in the abdomen and throat. The vomitus and feces may appear like rice water and be blood stained. The skin is clammy, there are cramps in the legs, and as the condition progresses, albuminuria, suppression of urine, and dehydration complicate the picture. Death may occur in a few hours to several days, or the patient may recover.

A *subacute type* of poisoning may develop if the drug is administered in small doses. The symptoms are prostration, dehydration, gastritis, albuminuria, anemia, dermatitis, and coma. Death occurs after weeks or months. Sometimes a patient, following an acute attack, develops a chronic neuritis, associated with anesthesia, paralysis, trophic disturbances, and loss of the hair and nails. Symptoms of chronic gastritis, anorexia, weakness, and general ill health may occur.

Post-mortem findings show an irritation of the gastrointestinal tract. There may be fatty changes in the organs and degenerative changes in the blood vessels. The fatal dose is about 3 grains.

TREATMENT OF ACUTE POISONING.—Treat by emptying stomach, and lavage; use warm milk and water for lavage. An emetic mixture of a teaspoonful of mustard and a tablespoonful of salt in a tumbler of water may be given. BAL (dimercapto) is now the treatment of choice. (See Organic Arsenicals, Chapter IX.) Ferric hydroxide with magnesium oxide, given in large amounts, is an excellent antidote for arsenic. There is formed a loose combination between the ferric hydroxide and the arsenic, thus limiting its absorption. Castor oil is indicated for cleansing the intestine. Sodium thiosulfate, in doses of 0.5 gram (7½ grains) by vein or 2 grams (30 grains) by mouth, has been recommended as a valuable antidote. Some recommend tincture of ferric chloride (15 cc.) and magnesia in a glass of water. Give colonic flushings of 4 grains of calcium sulfide to a pint of water. Opium may be administered to check vomiting and diarrhea; saline hypodermoclysis will stimulate renal elimination. Stimulants, such as digitalis, strychnine, caffeine, etc., may be indicated.

CHRONIC ARSENIC POISONING.—Symptoms of chronic poisoning may result from continual use of excessive doses of arsenic or from its prolonged absorption by those whose work or food brings them in contact with it. The medicinal use of arsenic, and the manufacture of arsenic sprays and of paper colored with arsenic pigments have occasionally caused chronic arsenic poisoning. Epidemics have occurred from drinking beer contaminated with arsenic, and from the use of certain cosmetics containing arsenic.

The symptoms vary with the route of introduction. At first the patient complains of weakness and anorexia, with nausea and vomiting of small amounts of mucus. Jaundice may be present. There is often a low fever. Skin eruptions occur frequently. There may occur skin modifications, such as overgrowth of the horny layer, especially of the palms and soles. Frequently there appears an arsenic melanosis. Anemia is a common result of prolonged use of arsenic. Multiple neuritis may occur; this generally involves the limbs rather than the trunk. Paralysis of sensation followed by motor paralysis is not uncommon. Optic atrophy has been observed.

TREATMENT OF CHRONIC POISONING.—Removal of the patient from all contact with arsenic will usually result in gradual disappearance of the

symptoms. BAL is administered as in acute poisoning. Removal of the arsenic in the system may be hastened by means of potassium iodide, saline enteroclysis, and purgation. The intravenous injection of 10 cc. of a 5 per cent sodium thiosulfate solution every other day is recommended to clear up skin lesions. Arsenical neuritis may be aided by massage and electric treatment. Strychnine may be given early in the disease. Treat symptomatically.

Tolerance and Habituation.—The habitual use of arsenic leads to tolerance; for example, if an animal is given a daily dose of arsenic, beginning with a very small amount and gradually increasing it, after some months many times the lethal dose may be given without any symptoms of poisoning. The peasants and mountain climbers of Styria and Tyrol indulge in arsenic habitually, believing it gives them more strength and endurance. Arsenic-eating has been indulged in by young women of some countries, including America, with the object of improving the complexion and the figure.

Therapeutic Uses.—For therapeutic purposes Fowler's solution (solution of potassium arsenite) and solution of arsenous acid are very useful. The odor of Fowler's solution is disagreeable to some patients and is less stable than the solution of arsenous acid.

BLOOD DISEASES.—Arsenic has proved of temporary value in the treatment of *pernicious anemia, leukemia,* and *Hodgkin's disease.* In these conditions it is best administered in the form of solution of potassium arsenite (Fowler's solution) or a solution of arsenous acid. Arsenic is the only drug of any value in the treatment of Hodgkin's disease. The nodes recede temporarily, but the ultimate course of the disease is not affected.

CHRONIC MYELOGENOUS LEUKEMIA.—Arsenic in the form of *Fowler's solution* may be used if the cells are relatively mature. The medication may be begun five to six weeks after x-ray therapy, and the dose increased from three drops three times a day after meals to as high as fifteen drops three times a day, unless symptoms of poisoning appear. Fowler's solution decreases both the red and the white cell counts, and in a patient with *leukemia* the white cells are reduced from 1,000,000 to about 10,000 and the red cells from normal to approximately 2,000,000. Arsenic also reduces the size of the spleen and liver.

Arsenic is an old and tried remedy in *pernicious anemia.* Fowler's solution or solution of arsenous acid may be given, beginning with 3 drops three times a day, and gradually increasing the dose to 12 or 15 drops three times a day.

SKIN DISEASES.—Arsenic is used externally and internally to improve the nutrition of the skin and hair. Many forms of skin diseases, such as psoriasis, chronic eczema and lichen ruber, have responded well to arsenic therapy. For example, in the treatment of psoriasis the solution of potassium arsenite, or Fowler's solution, in slowly increasing dosage of 1 to 10 minims, well diluted, three times daily for several months, is of value when other drugs fail. Arsenic trioxide, $\frac{1}{40}$ to $\frac{1}{20}$ grain, t.i.d., in tablet form or in the Asiatic pill is recommended by Ormsby. Acute inflammatory conditions of the skin may be made worse by arsenic.

In the treatment of *lupus erythematosus* a paste, consisting of arsenic trioxide and acacia, in equal parts, and a saturated solution of cocaine hydrochloride is spread over the diseased area, but no more than a square inch at a time should be treated.

Arsenic is used in the treatment of *warts.* The drug may be applied in the form of Fowler's solution, after the lesion has been softened with a 5 per cent solution of potassium hydroxide.

NERVOUS AND RHEUMATIC CONDITIONS.—Arsenic has been used with some success in *chorea, neuralgia, idiopathic epilepsy, arthritis,* etc. It is thought to be especially adapted to cases exhibiting a periodic character. In *chorea* it is given in rapidly ascending doses until, in a child ten years old, 2.1 cc. (35 minims) of Fowler's solution are taken or vomiting appears. In *arthritis deformans* arsenic must be administered early, if good results are to be obtained.

MALARIA.—Arsenic is used internally in the treatment of malaria. Patients with profound cachexia respond favorably to this treatment. In acute cases it acts favorably, but quinine is a more certain cure. In obstinate cases quinine therapy may be reinforced by arsenic, and, no doubt, the parasites which are least affected by one drug may be acted upon by the other.

MISCELLANEOUS DISEASES.—The majority of cases of *pellagra* are benefited by arsenic administration. Arsenic has been especially valuable in severe cases of *diabetes mellitus,* in combination with the usual measures. It may be used *externally* for the eradication of *superficial growths.* Marsden's paste, consisting of two parts of arsenic trioxide and one part of mucilage of acacia, may be used.

Asiatic pills, for psoriasis:

℞

Arsenii Trioxidi	0.13 Gm. (gr. ij)
Piperis Pulv.	8.00 Gm. (3ij)
Ext. Gentianae	8.00 Gm. (3ij)

M. ft. cap. No. lx.
Sig.: One after each meal.

For pernicious anemia:

℞

Arsenious Acid Solution . . . . . 30.00 cc. (f℥j)
Sig.: Begin with three (3) drops as directed.

Or

℞

Potassium Arsenite Solution	6.00 cc. (f3iss)
Aromatic Elixir q.s. ad	120.00 cc. (f℥iv)

M. Sig.: Teaspoonful with water after meals.

PREPARATIONS

Arsenic Trioxide, *Arseni Trioxidum,* U.S.P. (Arsenious Acid, Arsenious Oxide. Caution.—Arsenic Trioxide (As_2O_3) is extremely poisonous. *Dosage:* 0.002 Gm. (1/30 grain) in pills or solutions. B.P., 0.001-0.005 Gm. (1/60-1/12 grain).

Arsenious Acid Solution, *Liquor Acidi Arseniosi,* N.F. (Arsenic Hydrochloric Solution, Arsenic Chloride Solution.) Arsenic trioxide (1%) in diluted hydrochloric acid (5%) and distilled water. *Dosage:* 0.2 cc. (3 minims).

Arsenic and Mercuric Iodides Solution, *Liquor Arseni et Hydrargyri Iodidorum,* N.F. (Donovan's Solution). *Dosage:* 0.1 cc. (1½ minims). *Liquor Arseni et Hydrargyri Iodide,* B.P., 0.3-1 cc. (5-15 min.).

FLUORIDES

Sodium fluoride (NaF) is a general protoplasmic poison. It is used to poison cockroaches and rats and is thus of toxicologic interest. Sodium fluosilicate is also a poisonous substance.

Toxicology.—*Acute poisoning* is characterized by nausea and vomiting, abdominal cramps, cyanosis, tremors, and convulsions. Treat by gastric lavage, using calcium chloride solution in limewater. Calcium glyconate (10 cc. of 10 per cent solution) may be injected intravenously. Artificial respiration and external heat may be necessary.

The symptoms of *chronic poisoning* are mottled teeth in children, anemia, and slow growth. The source of poisoning is commonly found in drinking water, especially in the southwestern states. Treat by removing patient from source of poison. Administer milk or a high calcium diet. Dental consultations may be advisable.

Fluorine and Teeth.—The relation of fluorine to the teeth has created wide interest. Epidemiologic studies indicate that too little fluorine in the drinking water results in excessive dental caries; too much causes mottling of the teeth (fluorosis). Mottled enamel, or endemic dental fluorosis, is caused by excessive amounts of fluorides (more than 1.5 parts per million of fluoride) during the period that permanent teeth are calcifying.

As a result of recent studies demonstrating the decided inhibition of dental caries among users of domestic waters containing 1 part per million of fluoride or over, a number of studies have been directed toward the use of fluorine to prevent the development of caries. One of the methods employed is the topical application of a 2 per cent aqueous solution of sodium fluoride following prophylaxis. Studies completed indicate that after four treatments, spaced about a week apart, a reduction of about 40 per cent in the incidence of dental caries may be expected.

The mechanism of preventing dental caries is not known. It has been suggested that fluorine decreases the solubility of the enamel in acid. Others believe that it checks the growth of Lactobacilli, but there is no evidence that fluorine is effective after the teeth are fully formed. (J. Am. Dent. Ass. 34: 345, 1947.) However, fluorination of domestic waters is expected to reduce the incidence of new caries by as much as 40 to 60 per cent.

Fluorides in Dentistry.—The application by the dentist of a dilute (0.05 to 2.0 per cent) aqueous solution of sodium or potassium fluoride to the permanent teeth of children immediately after prophylaxis appears to have value as a measure for reducing the incidence of caries. (Council of Dental Therapeutics, 1948.)

The evidence in respect to the use of fluorides for the control of dental caries in adults is so limited and inconclusive that no statement can at this time be made as to whether it will or will not reduce the incidence of caries.

HELIUM

Helium, which is a noncombustible, colorless, odorless, inert gas, has a molecular weight of only 4 and therefore has a specific gravity of only one-seventh that of nitrogen and *one-eighth that of oxygen.* Helium, argon, krypton, neon, and xenon comprise the rare gases. Together they constitute about 1 per cent of the atmosphere. These gases are not essential to respiration. In 1934, Barach first used helium and oxygen in the treatment of lung diseases. Maytum, et al. (1935), reported favorable results in the use of helium in the treatment of severe asthma. Eversole (1938) reports its use in 110 cases, for relief of stridor or obstruction; 87 per cent obtained either complete or partial relief.

Action and Uses.—Helium provides an ideal vehicle for the administration of anesthetic gases. A mixture of oxygen and helium (79:21) is only one-third the weight of air; its ability to diffuse is inversely proportional to the square root of its molecular weight or approximately twice that of air.

Its mixture with oxygen in the same ratio as nitrogen-oxygen of the atmosphere is used as a less dense substitute for air that must be breathed under high atmospheric pressure. Helium-oxygen mixtures, because of the decreased effort required to breathe them, have been suggested to relieve various types of dyspnea and to overcome respiratory difficulty during inhalation anesthesia. The use of helium as an inert component gas of anesthetic-oxygen mixtures is limited to the extent by which it displaces oxygen required to meet physiologic needs. It is useful with cyclopropane mixtures to reduce inflammability.

Therapeutic Uses.—*Respiratory Obstruction.*—Helium is of value in obstructive conditions of the upper airway in which a general anesthetic has to be administered, e.g., in retropharyngeal abscess, glottis infections, and in edema of Ludwig's angina. Helium may be used with success in the suppression of *laryngeal stridor* during anesthesia. While the use of helium cannot replace the use of endotracheal tube, it forms a valuable means of passing to a state in which intubation may be performed. In some cases it may eliminate the necessity of performing a difficult intubation or furnish a means of avoiding tracheotomy. The use of these gases in proper proportion greatly benefits patients with such conditions as acute pulmonary edema, emphysema, pulmonary fibrosis, and asthma. The breathing of such a mixture makes it possible for a deep sea diver to be decompressed much more rapidly.

In conclusion, it can be said that the addition of helium to the field of pneumatology is one of great magnitude. It seems quite certain that helium therapy has definitely established itself in our drug armamentarium.

PREPARATION

Helium, *Helium,* U.S.P. Contains not less than 95 per cent by volume of helium, the remainder consisting mainly of nitrogen.

GOLD

Gold compounds are used with marked success in the treatment of lupus erythematosus and certain other skin diseases. It is acclaimed to be the best single therapeutic substance in the treatment of rheumatoid arthritis, but its use is limited as few rheumatologists and clinics have sufficient experience in chrysotherapy. Gold compounds have been used also in pulmonary tuberculosis and in asthma but with rather disappointing results.

Lupus Erythematosus.—Curative treatment is difficult, and should be in the hands of an expert. Gold salts have been used considerably; for instance, gold sodium thiosulfate, 10 mg. intravenously, weekly for two weeks, then 25 mg. weekly for two more weeks, and finally 50 mg. weekly thereafter until 1 Gm. or more has been given. The results are occasionally goood.

Rheumatoid Arthritis.—The results of gold therapy are not dramatic by any means. However, gold therapy produces notable results in perhaps one-third of the patients treated. The preferred compounds of gold are gold sodium thiomalate (myochrysine) and gold sodium thioglucose. Gold sodium thiosulfate is too toxic, and colloidal gold

preparations are useless as they are rapidly removed from the general circulation by reticulo-endothelial phagocytosis.

Start treatment with either of the above gold compounds, using a dose of 10 mg. weekly given intramuscularly. After two weeks, increase dose to 25 mg. for six to eight weeks, and then to 50 mg. per week. After 1 Gm. has been given, again increase the dose to 50 mg. twice weekly until 2 Gm. has been given. Relief may occur after 300 to 400 mg. have been given. If no improvement follows use of 1 Gm. of gold, abandon treatment.

Toxic reactions are stated to occur in 20 to 56 per cent of the cases, but with proper precautions this incidence may be reduced. The more common reactions are urticaria, dermatosis, minor rashes, and transient albuminuria. More serious symptoms include bone marrow depression with thrombopenia and granulocytopenia. Finally, parenchymal degeneration may appear in the kidneys, liver, or bowel.

Vigilant watch should be kept of the patient. Examine blood carefully before each of the first four injections. Then examine as frequently as possible, at least every two or three weeks. Examine the buccal mucosa and skin for lesions. Gastric upsets are indicative of toxicity.

Treatment by BAL has been most gratifying. Unfortunately, BAL also has toxic actions of its own (malaise, nausea and vomiting, pains in the legs, abdomen, and head, etc.). *Dosage:* Administer 0.25 cc. (10 per cent solution) per 10 kilograms body weight intramuscularly, repeated four times at intervals of four hours on the first two days, then twice on the third day and only daily on the next five days. (Total dose—2625 mg. BAL.)

From the reports now available, BAL therapy deserves further trial in the treatment of reactions caused by gold salts.

References

Histamine and Antihistamine Drugs

Blumenthal, L. S., and Rosenberg, M.H.: Diphenhydramine Hydrochloride (Benadryl Hydrochloride), J. A. M. A. **135**: 20, 1947.

Dragstedt, C. A.: The Significance of Histamine in Anaphylaxis, J. Allergy **16**: 69, 1945.

Feinberg, S. M.: Histamine and Antihistaminic Agents, Their Experimental and Therapeutic Status, J. A. M. A. **132**: 702, 1946.

Feinberg, S. M., and Bernstein, T. B.: Tripelennamine "Pyribenzamine" Ointment for the Relief of Itching, J. A. M. A. **134**: 874, 1947.

Levin, S. J.: B-dimethyl-aminoethyl Benzhydryl Ether Hydrochloride (Benadryl, Its Uses in Allergic Diseases), J. Allergy **17**: 145 (May), 1946.

O'Leary, P. A., and Farber, E. M.: Evaluation of Betadimethylaminethyl Benzhydryl Ether Hydrochloride (Benadryl) in the Treatment of Urticaria, Scleroderma and Allied Disturbances, Proc. Staff Meet., Mayo Clin. **21**: 295-297, 1946.

Wells, J. A., Morris, H. C., Bull, H. B., and Dragstedt, C. A.: Observations on the Nature of the Antagonism of Histamine by β-dimethylaminethyl Benzhydryl Ether (Benadryl), J. Pharmacol. & Exper. Therap. **85**: 122, 1945.

Protein and Amino Acid Preparations

Elman, R.: Intravenous Protein Nutrition, Physiol. Rev. **24**: 372, 1944; J. A. M. A. **128**: 659, 1945.

Elman, R.: Parenteral Alimentation in Surgery, New York, 1948, Paul B. Hoeber, Inc.

Hoffman, W. S.: The Clinical Significance of Proteins and Amino Acids in Surgery, J. Internat. Coll. Surgeons **10**: 492 (Sept.-Oct.), 1947.

Snake Venoms

Macht, D. L.: Experimental and Clinical Study of Cobra Venom as an Analgesic, Proc. Nat. Acad. Sc. **22**: 61, 1936.

—: Therapeutic Experiences With Cobra Venom, Ann. Int. Med. **11**: 1924, 1938.

Rottmann, A.: Zur Therapie der sensiblen Reizsymptome bei Tabes dorsalis durch Kobratoxin, Klin. Wchnschr. **16**: 1051, 1937.

Steinbrocker, O., McEachern, G. C., LaMotta, E. P., and Brooks, F.: Experience With Cobra Venom in the Arthralgias and Related Conditions, J. A. M. A. **114**: 318, 1940.

Fluoride

Council on Dental Therapeutics Reports on Topical Application of Fluorides, J. A. D. A. **34**: 700 (May 15), 1947.

Knutson, J. W., and Armstrong, W. D.: The Effect of Topically Applied Sodium Fluoride on Dental Caries Experience. II. Report of Findings for Second Study Year, Pub. Health Rep. **60**: 1085 (September 14), 1945.

Knutson, J. W., and Armstrong, W. D.: The Effect of Topically Applied Sodium Fluoride on Dental Caries Experience. III. Report of Findings for the Third Study Year, Pub. Health Rep. **61**: 683 (November 22), 1946.

Helium

Barach, A. L.: Use of Helium as a New Therapeutic Gas, Proc. Soc. Exper. Biol. & Med. **32**: 462, 1934.

Boothby, W. M., Mayo, C. W., and Lovelace, W. R.: Oxygen and Oxygen and Helium Therapy: Recent Advances, M. Clin. North America (Mayo Clinic Number) **23**: 977, 1939.

Gold

Comroe, B. I.: The Use and Abuse of Gold Therapy in Rheumatoid Arthritis, J. A. M. A. **128**: 848, 1945.

Ragan, C., and Boots, R. H.: The Treatment of Gold Dermatitides, J. A. M. A. **133**: 752 (March 15), 1947.

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