McGRAW-HILL PUBLICATIONS IN PHARMACY

Fundamental Principles
and
Processes of Pharmacy

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Fundamental Principles

and

Processes of Pharmacy

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FUNDAMENTAL PRINCIPLES AND PROCESSES OF PHARMACY

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Dedicated
to the educators,
members of the state boards of pharmacy,
and pharmacists
who have unselfishly striven in the past
and are yet endeavoring
to advance the profession of pharmacy
by the elevation of educational standards and requirements
and the enactment of legislation
for the protection and welfare of mankind

PREFACE

This book should serve to introduce the student of pharmacy to the professional subjects he will take up in his academic program. It is a manual or a guide to *introductory pharmacy.* This by its very nature should be, at least in part, of an orientative character, to assist the student to learn in a general way the professional and commercial aspects, requirements, and opportunities of pharmacy. A clear concept of what constitutes the profession should enable the student to determine whether he wishes to continue the course and to serve pharmacy effectively under its present limitations.

A decision on this basis would appear to be a sane and humane one for the welfare of the public, for the interests of the student, and for the benefit of the profession, since pharmacy cannot progress if practiced by persons who are unhappy in it or unprofessional in their attitude. If, as a result of this text, this decision and selection can be made early in the curriculum, then this volume has accomplished one of its primary purposes. With this in mind, the first chapters give a brief historical development of pharmacy and a statement of principles for its practice, discuss the literature essential to the maintenance of standards, describe the modern pharmaceutical curriculum, and outline the opportunities offered by the profession.

Some educators, no doubt, are of the opinion that orientative material is too advanced for the beginner in the pharmaceutical curriculum. The authors, however, as well as many others, are convinced that the principles embodied in the first chapters are so fundamental to the profession that they should be immediately impressed upon the new student and repeatedly emphasized throughout the educational program.

As a manual of instruction, this text offers the essential principles and techniques necessary for progressing to the more difficult courses which follow in logical sequence in the curriculum, in which it is expected that they will be elaborated upon more

fully and also applied. Study questions at the end of each chapter give the student the opportunity for a thorough review of the preceding material. The suggested collateral readings at the end of each chapter will help him to acquire a broader knowledge of the subject. The student is strongly urged to consult these, for it is realized that neither this book nor any other single work can serve as an adequate introduction to the subject of pharmacy.

A feature of the text is a pronouncing index, intended as an aid in bringing about greater uniformity in the pronunciation of pharmaceutical terms among members of the profession.

THE AUTHORS.

CHAPEL HILL, N. C.,
September, 1944.

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THE AUTHORS.

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FUNDAMENTAL PRINCIPLES AND PROCESSES OF PHARMACY

CHAPTER I

HISTORICAL DEVELOPMENT OF THE PROFESSION OF PHARMACY

It is not really what we accomplish in life, but rather what we stand for, that counts.—Emerson.

Mankind desires health and seeks in many ways to avoid sickness and disease. We of today live in an age of prevention and believe that an ounce of prevention is worth a pound of cure. Nevertheless, diseases, many of which are devastating, continue to plague us. There is evidence that disease is as old as life itself. Germs, and perhaps bacterial diseases, can be traced to the Carboniferous period, which, according to geology, was some 160 million years ago. Man, it is thought, did not appear on the scene until many millenniums later. With man came civilization and, without doubt, the spread of disease.[1] In his quest for health man seeks to conquer disease. This aim, perhaps, has stimulated more men to research activities than any other one factor.

Vitamins, a typical outgrowth of this research, are used both for their preventive and curative values. Serums, vaccines, and related products are used as medicaments to prevent and cure diseases and to aid in controlling epidemics. The scientific investigators have given us arsphenamines, the sulfonamides, penicillin, and many other valuable remedial agents. We have a right to expect that the future will bring many more remark-

[1] S. G. B. Stubbs and E. W. Bligh. "Sixty Centuries of Health and Physic," Paul B. Hoeber, Inc., 1931, Chap. I. Medical Book Department of Harper & Brothers, New York.

able medicinal products in the interest of health and the conquest of disease and that pharmacy, as a profession, will have a part in these discoveries.

Medical Practices of Primitive People.—It is not easy to learn of the medical ideas and practices of prehistoric man. The medical and hygienic practices of our present-day primitives, however, afford a sound basis for speculation.

Primitive people seem always to have been in awe of the forces of nature, such as wind, lightning, thunder, rain, hail, and snow. Doubtless they were even more in fear of diseases and looked upon them as evil forces or forms of hostile magic. They resorted to magic to rid themselves of the affiictions that beset them. This was quite natural, for the world, as they knew it, swarmed with invisible spirits causing disease and death.

Magic served primitive men in many ways, even in their search for daily bread. Primitive practices of medicine were usually associated with religious beliefs. Where there was magic, there were magicians and sorcerers, all too willing to perform magical tricks in an effort to relieve their suffering patients. The magician, whether god, hero, priest, king, prophet, or physician, was, to the savage, the medicine maker. In spite of magic and superstition the primitives of all ages have, through painful experience, acquired a considerable amount of useful and sound medical information.

Sumerian, Babylonian, and Assyrian Medicine.—The Sumerians had a well-ordered civilization in Babylon soon after 5000 B.C. They were familiar with many drugs and had a knowledge of hygiene, agriculture, and craftsmanship. Health was a subject of much importance to these people. This is evidenced by the fact that Hammurabi, the great lawgiver of Babylon, in boasting of how much he had accomplished for his people said, "I have brought health to the land."[1]

Of the 12,000 tablet fragments of Assyrian and Babylonian origin in the British Museum, 660 are said to be of medical interest. The medical texts show a considerable knowledge of medicine and therapeutics. Inasmuch as the Babylonians held closely to the demoniac idea of disease, it may be assumed that divination and incantation were associated with their medical

[1] *Ibid.*

practices. It is known that the Babylonian magician and physician were different persons and that the physicians sometimes called upon the magicians to aid them in the treatment of certain ailments. If certain features of medical magic were disgusting, this was for the purpose of displeasing the demon that caused the disease.

Many strange devices were considered to have great merit in treating the sick. Amulets and charms were worn upon the person. The sacred number seven was supposed to have much influence. However, many simple remedies were understood and used, such as enemas, poultices, bandages, plasters, compresses, salves, and liniments.

While the Babylonians held strongly to the demoniac idea of disease, the Assyrians believed that illness was, in part at least, punishment for the breaking of some law or taboo. The Jews considered it to be an expression of the wrath of Jehovah.

Such beliefs constituted a great hindrance to the development of the medical sciences by the ancients. Even so, progress was made in the field of medical knowledge, especially in public hygiene as practiced by the Jews. The Jewish observance of the seventh day of rest, the Sabbath, was a custom of great religious significance and was also valuable from the standpoint of health and hygiene. It is equally significant in our own day.

The Hebrew priests were charged with the enforcement of hygienic measures of living. They understood the contagious character of leprosy and the social diseases and enforced certain laws of segregation for those who were afflicted. They resorted to extreme measures of disinfection with respect to houses and, in some cases, burned the patient's clothing. The Jews were so modern in some of their hygienic and sanitary regulations that they have furnished a model for succeeding generations, even to the present day.

Egyptian Medical Practices.—The Egyptian physician was a man of high position and repute. Egyptian medicine has always been held in respect, and yet it was not divorced from religion.

There were many gods in Egypt. Thoth was the great god of healing and was considered to be skilled and all-powerful. Anepu was the apothecary of the gods of Egypt. He held positions of

great importance, being the "keeper of the house of medicine and chamber of embalmment" and the "apothecary and the compounder of prescriptions for the gods."[1]

The gods of Egypt were appealed to singly and collectively to give force to the curative effects of medicines. The great Ra, it is said, who was a compounder of drugs, once attempted to mix a cure-all for himself, but it failed him. He then sought the aid of lesser deities, the only result being a severe headache. Isis, a woman doctor, came to his rescue by not only curing his headache but relieving him of "all sufferings and evils of any sort."[2]

The mummification practices of the Egyptians have left many well-preserved specimens for observation. By studying these, scientists have been able to form a reasonably clear picture of the afflictions of these people. This is especially true of cranial, spinal, long bone, and dental conditions. It is known that arthritis was a common ailment among the Egyptians. Dental diseases were widespread among the later leisure class. Operative dentistry was unknown to them, and they must have suffered greatly.

The god-priest-physician relationships of the Egyptians were of great importance, for they believed that the gods knew the medicinal properties of herbs and plants and that this knowledge was transmitted to the priests. The people went to the priests and the temples for treatment and worship.

While the Egyptians were advanced in the knowledge of science, their pharmacy and materia medica contained many items that are questionable and nauseous. A detailed account of this phase of Egyptian medical history may be obtained by reading "The Papyrus Ebers."[3]

However, it is clear that the ancient Egyptians were skilled in the practice of pharmacy. They knew many chemical processes, the art of embalming, and methods of preservation. The art and science of chemistry, it is thought, originated in Egypt.

[1] A. H. Buck. "The Growth of Medicine from the Earliest Times to About 1800," Yale University Press, New Haven, Conn., 1917.

[2] C. P. Bryan. "The Papyrus Ebers," D. Appleton-Century Company, Inc., New York, 1931.

[3] *Ibid.*

Greek Medicine.—It is stated by medical historians that the origin of modern medicine is to be found in Greek medicine. "It has come down to us, in a direct line, through the sheer force of its inherent excellence, and with little or no aid from outside sources."[1] Homer's "Iliad" and "Odyssey," about 1194 B.C., give evidence of a comparatively advanced state of anatomy and medical treatment. Aesculapius and his sons Machaon and Podalirius are mentioned as having served in the expedition against Troy as surgeons to the army and as leaders of the troops. It is established that Aesculapius was a historical character who was deified in 420 B.C. He is reputed to have been the son of Apollo, the god of medicine, and to have been taught the art of healing by Chiron, one of the centaurs. Besides his two famous sons, mentioned above, he had four daughters, two of whom were Hygeia and Panacea.

Temples were built in honor of Aesculapius, and in them the the art of healing was practiced. They were convenient places to which people could go for treatment and rest. These temples, in the early years of their existence, were in the hands of the descendants of Aesculapius. The original Aesclepiadae kept the medical secrets and pharmaceutical formulas within the family leaders, who were both priests and physicians. Much attention was given to the location of the Aesculapian temples. The buildings and the surroundings were made attractive. The unclean and those about to die were not admitted to the temple enclosure. Simple curative measures, such as massage, dietetics, pure water, sunlight, pure air, and physical exercise, were a part of the rational treatment afforded at these centers.

Since it was not possible for all the sick to be cared for at the temples, there were traveling physicians who went about the country. They established outpatient clinics and institutes of healing not unlike our modern hospitals. Physicians, military doctors, general practitioners, and special medical attendants became common and led to the breakdown of the earlier priestly character of medicine. Medical schools were founded, among them being famous ones at Kos, Cnidus, and Rhodes. Hippocrates, the most renowned character in medical history, was a graduate of the school at Kos. He rationalized medicine,

[1] BUCK. *Op. cit.*

systematized medical knowledge, and put the practice of medicine on a high, ethical plane. The so-called "Hippocratic oath" is a most impressive document in medical ethics (see page 57). While the modern mind cannot accept all the practices and theories of Hippocrates, there is no reference in his writings to charms, incantations, divinations, and astrology. The theories of Hippocrates were distorted by his successors. However, Alexander the Great founded the city of Alexandria in Egypt in the fourth century B.C., and there the best in Greek medicine thrived for a time.

Great men contemporary with Hippocrates were Socrates, Plato, and Aristotle. Aristotle created the sciences of comparative anatomy, systematic zoology, embryology, botany, and physiology. Dissection of the human body was still taboo, and Aristotle admitted that the "inward parts of man are known least of all."[1] Theophrastus, a student of Aristotle, advanced the science of botany.

One of the greatest names in medicine after Hippocrates is that of Galen (A.D. 130–200), who was famous for his work in anatomy and physiology. It is said that he approximated the discovery of the circulation of the blood. His views were essentially those of Hippocrates. He traveled a great deal, collected many plants, and had much faith in drugs. Galen was the last of the Greeks to make noteworthy contributions to medicine, and for many centuries his reputation was a commanding one.

There were many other Greeks who were famous in the field of medicine. Empedocles, in the fifth century B.C., was the first comparative anatomist. Diocles, in the fourth century B.C., was author of the first Greek herbal and the first book on anatomy. Herophilus (about 300 B.C.) is called the father of anatomy, and Erasistratus (about 360 B.C.) is called the father of physiology. The latter were both connected with the school at Alexandria.

The Greek physicians prepared their own medicines. These were administered by their pupils, who remained with the patients, reported the symptoms, and carried out the doctors'

[1] J. J. MULLOWNEY. "The History of Medicine in Brief," published by the author, Nashville, Tenn., 1929.

orders in other ways. Prescriptions were few, crude, and simple. Pharmacy, in Greece, was closely associated with medicine in that physicians did much of their own compounding and dispensing. There was a class of root diggers known as the rhizotomes (*rhizotomoi*). They gathered and prepared their drugs with much mystery and according to superstitious rites. When the rhizotomes prepared compound remedies, they became known as the pharmacopoles (*φαρμακοπολοι*). The field of medicine in Greece about 300 B.C. became divided in practice among physicians, surgeons, rhizotomes, and pharmacopoles. The pharmacopoles were much like physicians of our time.

The physicians left surgery, which was beneath their dignity, to the surgeons. Compounding was left to the pharmacopoles. The physicians wrote out their directions for the guidance of the pharmacopoles, who did the compounding. Later, prescriptions became more complicated, and compounding them was not easy. The famous *theriaca* of Mithridates contained 54 ingredients. Many of the celebrated formulas for the *hierae* contained almost as many ingredients and must have required no little pharmaceutical skill to prepare.

When Rome conquered Greece, Greek medicine was taken to Rome, where it finally displaced the old Roman religious medical practices. In the hands of Dioscorides, Aretaeus, Galen, and Celsus, medicine made substantial progress in Rome at about the time of the beginning of the Christian era. Dioscorides was known for his materia medica. Aretaeus was a clinician and reported many observations of value upon pneumonia, tetanus, empyema, epilepsy, and insanity. Celsus was not a physician but a wealthy patron of science.

Medical and Pharmaceutical Practices in Rome.—The Romans at no time had a system of medicine of their own. Whatever professional development there was that was worth while medically may be attributed to the Greeks. For the Latin, every disease had a minor deity. Medical treatment consisted in satisfying and placating, in a businesslike way, the evil spirits presumably involved. The head of the house not only was supreme in his own household but was his own physician and health officer. The household included the slaves and all domestic animals.

The medicine cabinet of the Roman household contained a few simple herbs, which were purchased from merchants. There were no pharmacists as we know them today. The chief of the household knew a great deal about the use and application of drugs. The Roman system of medicine consisted not only in administering drugs but in observing the rites of mystery and magic.

It was difficult for science or rationalism to affect a system of religious folk medicine such as existed in the Roman Empire. The Romans were much more superstitious than religious. Powerful evil spirits and annoying goblins plagued every household. To treat a disease, it was necessary to use the proper magic to appease some angry god. If the treatment failed, this was only because the game had not been played right.

The Roman had a household god for almost every disease known to him. In the later Roman period, itinerant Greek physicians migrated to Rome and offered their services for a fee. They were mistrusted and looked upon as poisoners and assassins, for the Romans were not used to a professional attitude toward disease, for reasons already given. The elder Pliny is quoted as saying that they (the Romans) had "got on for 600 years without doctors." Their temples, with the priests in attendance, served as sanitariums and places where the weary and ailing could rest and recuperate. Without the influence of the medical practitioner these institutions never developed to any extent. In the late Roman period several notable Greek physicians were known to have served with the Roman armies. Galen had such an experience.

The Romans were so steeped in superstition that they looked upon even their herbs with awe. They believed in the efficacy of drugs but had no scientific basis for such a belief. In gathering their herbs, they gave much attention to form, color, odor, and other features. In making them into decoctions, they recognized all sorts of mystical influences. It was necessary to observe the seasons of the year, phases of the moon, hours of the sun, and the position of other heavenly bodies during the time of gathering. Conditions of cold, heat, and moisture and other meteorological phenomena had also to be taken into account. Saint's days, the beginning of spring, and the ending of autumn were times to be

considered in gathering, culling, and brewing herbs. The head of the Roman household bore great responsibilities in a medical way, and it may be assumed that he called upon the priest, the herbalist, and the astrologer for much advice and help.

Magic and occultism formed the framework of Roman medicine. The priests held high places as mediators and interpreters of the oracles and mystical experiences of the people. The Romans believed in holy wells, the fantastic notion of signatures, incantations, the potency of names, the laying on of hands, talismans, and symbolisms of all sorts.

Rome had more than her share of medical quacks. The physicians were not, at any time, a professional group. They did much to bring medicine into contempt. But poorly trained and ignorant as they were, on the whole there were many among them who were honest, skillful, and helpful.

Arabian Pharmacy and Medicine.—In conquering Persia, Asia Minor, northern Africa, and southern Europe, the Moslems fell heir to the culture of those whom they had overrun. The Arabs conquered Persia about A.D. 650, and there they came in contact with the Nestorian Christians, who had kept Greek art and science alive. Their Greek texts were translated into Arabic; hence, Greek culture and Arabic learning were fused. After the fall of Rome in A.D. 476 the culture drift was east toward Byzantium, the center of which, for several centuries, was Constantinople. The Arabs spread their new learning throughout their empire and brought it west again, where it was localized in the Spanish cities of Córdoba, Toledo, Seville, and other centers.

Bagdad became the capital of the Eastern Caliphate in the sixth century A.D. The monarchs were friends of learning, especially of science, medicine, and pharmacy. They encouraged and supported the collection, copying, and translation of Greek manuscripts of all sorts. As a result, the works of Hippocrates, Galen, Dioscorides, and other famous authorities were translated into the Arabic language. These translations preserved for us many of the Greek classics that otherwise might have been lost. The Arabs were not original in their science and culture but studiously mastered the medical and pharmacal teachings of the Greeks and later brought this medical heritage into Sicily and

Spain. In this respect, their custodianship was of great value to the learning of the West. It was in the cities of Spain that the Arabic language and culture met the Latin scholar. The Arabic texts were translated into Latin, indirectly exposing Europe to Greek thought. The Latin scholars recognized the source of Arabic culture and felt that they themselves had better sources of information and learning than the Arabs. The latter, by their zeal for learning, reawakened the Latin West. This, in the end, led to the undoing of the Moslems in Spain. There remains in Spain, even today, evidence of Arabic culture and science.

The pharmacy and medicine that the Arabs preserved and developed were a curious blend of Greek medicine, derived from the Nestorian Christians, Jewish medical practices, astrology, and the occultism of Egypt and India. Arabian medical culture lasted from the eighth to the twelfth century. It was dominated by Greek thought in the earlier centuries but later developed some independence.

Even though the Arabian medical scholar had inherited the best that Egypt, Greece, and Rome had left, he often gave first place to unimportant things. His professional status was apt to be gauged more by the height of his turban and the length of his sleeves than by his skill and learning. He was not versed in anatomy, believing, for example, that the liver guards the heart and is the seat of the soul. Dissection was forbidden because of certain religious convictions. Surgery was left to wandering specialists and obstetrics to midwives. Arabian physicians wrote charms and mystified their patients with all sorts of tricks in an effort to enhance their importance and authority. They were strongly interested in collecting their fees and often stipulated the amount in advance.

Hospitals in Arabia.—Many hospitals were built and kept up by the Arabs. One of the best of these was founded at Damascus (1160) and another at Cairo (1276). The hospital at Damascus gave treatment and free drugs to needy patients for more than three centuries. The great Al-Mansur hospital in Cairo employed both men and women as nurses and had separate wards for certain diseases. It had, among other things, diet kitchens, outpatient clinics, a library, lecture rooms, and wards

for women. The convalescents, upon being discharged, were given money so that they need not return to work too soon. In Córdoba and other Spanish cities, under the Moslems, there were hospitals much in advance of anything the rest of Europe had. The Moslems were also kind to the insane, a practice that Latin and European Christians had not developed.

Arabian Pharmacy.—In the eighth century, Arabian pharmacy and medicine became separate branches of learning and practice. The separation was made compulsory by law in the eleventh century. Arabian pharmacists imported drugs, such as senna, camphor, rhubarb, musk, cloves, aconite, and mercury, from many sources. Arabian apothecary shops were regularly inspected and severe punishment meted out to those who sold spurious drugs.

Alchemy is said to have been the child of Arabian medicine. Along with ideas of alchemy there was developed the idea of a polyvalent "elixir of life," a cure-all. This elixir was assumed to be a "potable gold." In searching for it, aqua regia and other strong acids were discovered. This was, perhaps, the beginning of pharmaceutical chemistry.

Arabian Scholars.—Arabia did not produce many outstanding scholars. The following should, however, be mentioned. Rhazes (865–925), according to Garrison,[1] ranks with Hippocrates, Aretaeus, and Sydenham. His descriptions of smallpox and measles are considered to be classic because his accounts are so vivid and complete. "Continens," his encyclopedia of medicine, which has been preserved in Latin, has many original clinical histories and therapeutic experiments.

Ali Abbas (about 994) was the author of the "Royal Book," a treatise on medicine. It was translated into Latin about 1070–1080. The anatomical section of this book was the text at Salerno until 1170.

Avicenna (980–1037) was called the Prince of Physicians. He is credited with having written over one hundred works upon many subjects. He first described the properties of sulfuric acid and alcohol. His "Canon" was a great storehouse of medical knowledge which, according to critics, did much harm in

[1] F. H. GARRISON. "An Introduction to the History of Medicine," W. B. Saunders Company, Philadelphia, 1929.

that it dominated European medicine for too long a time and thus stultified it.

Avenzoar, a Cordovan, died in Seville in 1162. He described the itch mite and serous pericarditis, inflammation of the middle ear, and other ailments.

Moses Maimonedes (1135–1204) was one of the last of the eminent scholars of the Arabian era. He wrote a treatise on personal hygiene and was an authority on poisons.

The Arabs did much to improve pharmaceutical products and to make them more elegant and palatable. Their pharmacy and materia medica have lived through the ages.

Byzantine Pharmacy and Medicine.—The Eastern Roman Empire survived the Western Empire by a few centuries. Byzantium, later known as Constantinople, was its capital and became the center of the Byzantine Empire. It not only absorbed the shock of the falling empires of the West but withstood, for a time, the impact of Arabia, which was the rising power of the Mediterranean. Scholars who had been trained at Alexandria in pharmacy, medicine, and other branches of learning gathered at Byzantium. They were familiar with the culture of the Greeks and the Romans and traveled both east and west from this more advanced intellectual center. Arabia profited by those who traveled east. The West, even beyond Greece and Rome, benefited by those who ventured to explore the old centers of civilization and carry their learning into western Europe.

The scholars of Byzantium were not keen scientists but were good copyists and encyclopedists. They thus had a considerable share in preserving the learning of the Greeks and Romans. But though Byzantium conserved and preserved its inheritance, it remained static. Here the mysticism of the East met the philosophies of the West, and the voice of wisdom was heard too seldom. Demonism and symbolisms of many sorts hindered intellectual development even more than in earlier ages.

Among the few prominent Byzantine physicians was Aribasius (A.D. 325–403). He was a great compiler and left a catalogue of early Greek physicians who otherwise might have been forgotten. His "Encyclopedia of Medicine" comprises over seventy volumes and deals with all aspects of the subject. He spoke well of

Galen. His "Euporista" was a medical treatise popular during the Middle Ages. He has been regarded as the founder of pedagogics and rated as the best medical writer of the ancient world.

Aretius (sixth century A.D.) was trained in Alexandria and was the most learned of the later writers upon poisons. His compilations upon medicine, pharmacy, and toxicology have come down to us nearly complete. He gave good accounts of many ailments such as headache, pleurisy, and epilepsy, with accurate treatments for them. He recommended many salves and plasters.

Alexander of Tralles (A.D. 525–605) wrote prescriptions and first recommended the use of rhubarb. Although he used bleeding as a treatment, he was an advocate of fresh air, baths, a milk diet, and natural means of recovery from illnesses. His work, known as "Practica," rivaled the best thought of Hippocrates and Galen. He was widely traveled and finally settled in Rome.

Paul of Aegina (A.D. 625–690) was the last of the Greek eclectics and the best of the Byzantine scholars. His "Epitome of Medicine," in seven books, was the accepted standard for a long time. He was well versed in eye surgery and summarized all that was known of pediatrics and obstetrics from antiquity to his own period; thereafter, up to the Renaissance, there were no considerable developments in these fields. From his time on, Byzantium was nonproductive as a medical center.

Pharmacy and Medicine of the Middle Ages.—The Middle Ages, or Dark Ages, are the thousand years extending from the time of Galen to the Renaissance. Galen revived the clinical common sense of Hippocrates. The medical outposts that he established have been discussed earlier in this chapter. But almost everything that Hippocrates and his faithful followers gave to the sciences, especially medicine, was all but shrouded from view during the Dark Ages.

However, though the light of Greek medicine faded during this period, it was never entirely extinguished. The Greek culture and language prevailed at Constantinople, the last remnant of Roman dominion, for many centuries after the fall of the Western Roman Empire. The Goths and Huns invaded Rome from the north. The Arabs attacked impregnable Constantinople from the south and pushed on past it, invading

and threatening western Europe. But when they were finally driven out of Spain, there were left the science and learning of the Arabian and Jewish physicians. Moreover, the Arabs served as the saviors of learning because they kept Greek thought alive through "all these years of the twilight of culture."[1]

The crusaders who survived and returned to their homeland carried with them the leaven of Greek thought that they had found in their travels. In addition, Europe became heir to Greco-Arabic learning through the work of translators, who were especially active in Spain. The Arab bowed to the medical theories of Galen and the earlier Greeks and, as a consequence, made no advances in anatomy. Nevertheless, the profession of medicine rose to a position of dignity and importance.

Medical culture might have been lost except for the fact that a center of medical learning was preserved at Constantinople. In addition, the clergy became the custodians of medical knowledge. This phase has been referred to as *monk medicine.* The Benedictine order of monks taught that the care of the sick is a Christian duty. Monkish schools made the teaching of medicine a part of their discipline. Thus, throughout western Europe, medicine was in the hands of the clergy for a time. While little or no scientific progress was made, old texts and the holiness of medical art were preserved.

Medical Schools.—Under the Romans, it was possible for physicians to be teachers. Salerno, located about thirty miles south of Naples, was a health resort in the period of Roman supremacy. It was here that St. Benedict founded the hospital of his order in A.D. 539. Salerno became the center of a guild of physicians that attracted patients and students from other places. Later a school of medicine was established, probably the first in Europe to resemble a university. It served as a link between the later Greek physicians and the institutions of our own time, existing for nearly a thousand years. It was at the height of its influence in the twelfth century, when it was the leading educational center of Christendom. During the first crusade in 1096, the base hospital for the militant Christians was located at Salerno. The school was abolished by Napoleon in 1811.

[1] M. G. SEELIG. "Medicine, an Historical Outline," The Williams & Wilkins Company, Baltimore, 1931.

Greek medical teaching was transplanted to Salerno. Anatomy as a subject of study was much restricted. Surgery, which had advanced under Hippocrates and Galen, now degenerated into the use of cautery, plasters, salves, and drugs. Pharmacology was diligently fostered, and dietary measures were stressed, as also were materia medica and bedside manners. Students of medicine were taught the importance of reassuring the patient as to his welfare but to report doubt as to the outcome of his illness to his relatives. The mention of these ideas should indicate that modern medicine inherited much that is psychologically and practically sound.

Regulations Concerning Pharmacy.—The Magna Charta of the profession of pharmacy was issued in 1240, when Frederick II, head of the Holy Roman Empire, issued an edict creating pharmacy as an independent branch of public welfare service. Later, there were two additional regulations. These three became effective in Latin Europe but not in the Anglo-Saxon world. The regulations separated the practice of pharmacy from medicine and acknowledged "the fact that the practice of pharmacy required special knowledge, skill, initiative, and responsibility in order to guarantee adequate care of the medicinal needs of the people."[1] Furthermore, official supervision was given to pharmaceutical practice, and the use of a prescribed formulary was made compulsory. The two sections of the law that were not accepted generally pertained to (1) the limitation of the number of pharmacies and (2) the fixing of prices for remedies by the government. The former of these was made operable in Germany, and the latter in the United States by our laws regulating minimum prices for pharmaceutical items.

With these regulations, pharmacy became a profession and its practice was placed upon a higher ethical plane. The following paragraph summarizes the situation concerning pharmacy from antiquity to the thirteenth century:

> Thus, Pharmacy, with its beginnings in the instinctive defense against disease by primitive peoples, developed under several diverse influences. As a part of the work of priests at first, it later fell among the duties of physicians. It found its own form and expression in the culture of

[1] E. KREMERS and G. URDANG. "History of Pharmacy," J. B. Lippincott Company, Philadelphia, 1940.

Greece and Rome and developed a kind of professionalism in Byzantium Only under the influence of Arabian wisdom and control, however, did it take firm root in European soil as an institution of public welfare to be respected, regulated, and further developed.[1]

Precursors of the Renaissance.—When Rome fell in A.D. 476, learned men scattered to other centers of culture. As has been indicated, the Arabs were the great preservers of the scientific, medical, and philosophical knowledge of the Greeks and Romans. In western Europe, medicine was in the hands of the clergy. The old texts were preserved, but little or no progress was made in this science for several centuries. Because of certain medical abuses by ignorant monks, in the eleventh century, the church forbade the teaching, studying, and practice of medicine by the higher clergy. This order was not obeyed entirely because the spirit of reformation was rising. Scholars at Salerno taught that medicine was a discipline based upon natural laws. There was an effort to correlate this new science with the tenets of the church. The medicophilosophical discussions that resulted were poor preparation for meeting the pestilences and scourges that visited the people later.

Education in western Europe was perhaps at its lowest ebb during the ninth century. This period was followed by a revival of learning in the eleventh to thirteenth centuries and the Renaissance in the fifteenth and sixteenth centuries.

There were many factors during these centuries to slow the progress of medicine. It was an age of faith healing. Superstitious practices were the vogue, and innumerable absurd objects were worn as charms, talismans, and amulets in an effort to ward off diseases. Where senseless drugs had failed, it was quite natural that the people should turn to holy charms. In England, in 1042, Edward the Confessor instituted the royal touch, which Henry VII made into an elaborate church ceremony. The royal touch, which was credited with the power of healing diseases, was practiced by a succession of kings and queens; it was treason to speak disparagingly of it. William of Orange, in 1688, abandoned the custom. This is the first mention of England in connection with the ancient medical practices of Europe. While the pharmaceutical practices of England were

[1] *Ibid.*

different from those of Continental Europe, progress in the sciences, medicine, and philosophy was about the same.

In the centuries immediately before and after the time of Christ, the people were steeped in superstitious beliefs of all kinds. Twelve hundred years later, Roger Bacon, like Galen and Hippocrates, believed that a knowledge of the stars was essential for physicians. "Wherefore a physician who knows not how to take into account the positions and aspects of the planets can effect nothing in the healing arts except by chance and good fortune."[1] Medieval physicians studied the horoscopes of their patients to aid in diagnosis and prognosis, as blood counts and X rays are used today. Shakespeare and Cromwell believed in witchcraft and astrology, and the descendants of the Pilgrim Fathers put witches to death in New England.

The full reign of superstition, however, was gradually undermined. There were those who doubted and questioned the current theories with respect to the causes of diseases and the remedies used to treat them. Emancipation from the old ideas came gradually and was aided greatly by the establishment of universities and the invention of the printing press. The rise of medical schools at Naples, Palermo, and Montpellier overshadowed the prestige and influence of Salerno. But, in the main, there was little medical progress in Europe during the Dark Ages. Haggard says, "To find any notable progress arising from medicine in these years we must turn to one branch of it—pharmacy—and to a progress that is essentially social rather than medical—one of enormous benefit to mankind. For the pharmaceutical beliefs of the times led to exploration and resulted in great geographical discoveries—including that of America."[2]

In the reaction to the domination of the church in medicine and to the philosophy and mysticism of the Dark Ages, three important characters should be mentioned. They were Roger Bacon (1214–1294), Arnald of Villanova (1240–1311), and Petrarch (1304–1374). Roger Bacon, the English philosopher,

[1] A. NEWSHOLME. "Evolution of Preventive Medicine," The Williams & Wilkins Company, Baltimore, 1927.

[2] H. W. HAGGARD. "Mystery, Magic, and Medicine," Doubleday, Doran & Company, Inc., New York, 1933.

was educated at Oxford and later taught there. He was a reformer and an independent thinker and insisted upon observation and experiment. He was a realist and attacked the false doctrines of his times, which, he maintained, were halting all progress. He was charged with heresy by the church and, although he in no way opposed the church, spent most of his life in prison. Arnald of Villanova, said to have been born in Spain, studied medicine at Montpellier and was instrumental in bringing about reforms in medicine. He was an experimenter and out of sympathy with the scholastic spirit of the church. He was charged with sorcery and forced to flee from Spain. He had a broad knowledge of science and did much to rationalize medical science. Petrarch, the Italian poet, aided in the process of rationalization by his poetic irony and philosophy.

There were other stimulating thinkers and reformers who helped to prepare the way for the Renaissance. These scholars, at least some of them, believed in returning to the Hippocratic ideals of cleanliness in surgery. As a consequence of their reforms, anatomy and surgery were greatly improved. The work of Guy de Chauliac (1300–1368), a Frenchman and the most distinguished surgeon of the fourteenth century, is regarded as evidence of the stimulation generated by the reforms.

The Renaissance.—The Renaissance (1453–1600), which followed the Dark Ages, brought a return to free thought and criticism. Among the influences that hastened this development were the introduction of the use of gunpowder and firearms, which eventually brought an end to feudalism, and the invention of the printing press, which, by the wider dissemination of information, made self-education more easily attainable. The three great medical leaders of this era were Paracelsus, Vesalius, and Paré.

Paracelsus (1493–1541), a Swiss alchemist and physician, publicly burned the works of Galen because he thought that they lacked authority. Although forceful and ingenious, he allowed alchemy, superstition, and much of the nonsense of his day to color his work. He was an itinerant doctor and learned much in traveling about Europe. He defied authority and was very contentious. Paracelsus was regarded by some as a charlatan in that he laid claims to having discovered the elixir of

life. It did not prolong his length of life remarkably, for he died in his forty-eighth year. He was the founder of chemotherapy and taught the use of sulfur, lead, mercury, antimony, iron, and other metals in therapeutics. He is regarded as an erratic genius who exercised the most profound revolutionary influence upon medicine and pharmacy of any man in history. Until his time, the causes of diseases had been ascribed to many sources; Paracelsus believed that they were due to natural causes and advocated a return to the teachings of Hippocrates.

Andreas Vesalius (1514–1564), as a boy in Belgium, displayed a passion for dissecting rats, mice, and other animals. He studied medicine in Paris, concentrating upon anatomy, and discovered errors in the teachings of Galen. He later taught surgery and anatomy at Padua and in 1543, against the advice of friends, published his studies in which he pointed out the errors of Galen. This brought him much glory as well as protests sufficiently vigorous to cause him to leave Padua. He then spent years as court physician to Charles V and Philip II. Vesalius was pre-eminently an anatomist. His work aroused much opposition, and denunciation by his former teacher duBois (Sylvius), but it had a profound influence upon the progress of surgery and medicine.[1]

Paré (1517–1590) was a French barber-surgeon. At the age of nineteen he became an army surgeon and had the opportunity to gain much knowledge about anatomy and surgery. His pleasing personality and genius for surgery brought him great honor. He discredited the therapeutic value of comminuted mummies and unicorn horns before the faculty of the University of Paris, and rationalized the treatment of wounds, especially those received in battle. He was influential in causing surgery to be placed in the hands of persons trained for this work. Many of the surgical practices of today originated with Paré.

The accomplishments of these men would indicate much progress in their respective fields. In order that students may not receive the wrong impression concerning the real situation with respect to medicine during the Renaissance the following statement from Haggard is cited:

[1] SEELIG. *Op. cit.*

In considering only such men as Paracelsus, Vesalius, and Paré, one obtains a false impression of the virtues of Renaissance medicine; these men stood almost alone. They are not representative of the medicine of the time. The practice was in the hands of those whose medical knowledge was little better than that of the rude empirics of the middle ages. Even the wealthy were treated by physicians who made diagnoses by inspection of urine, by astrological observations, or by palmistry, and who prescribed according to ritual and placed great hope in amulets and charms. Surgery was in the hands of barbers and executioners or in those of mountebanks and vagabonds who moved from town to town to escape the consequences of their acts.[1]

Pharmacy had held a respected position in the field of medicine long before the Renaissance. While the concepts of sicknesses and the causes of diseases were changing, the materia medica, especially as it might apply to home medication, remained fairly constant. Changing theories did not result in new drugs, as is often the case today. New combinations of remedies might be called for, or perhaps the usefulness of certain remedies questioned, or the use of old and tried remedies justified. Paracelsus advanced chemotherapy by introducing chemicals for internal medication and sought new and better ways for preparing his quintessences, which were tinctures or liquid extracts containing the essential virtues of the extracted drugs. This was in line with his theory that disease is due to a disturbed condition of the chemistry of the body; this condition, he said, can be corrected by the wise use of the proper chemicals. This appears to be good reasoning, but much of its force was lost because Paracelsus held to the belief, common in his day, that a mysterious force, or vital principle, dominates the functions of life. It was an act of heresy for Paracelsus to discard the feeble herbal medicaments of Galen and to advocate the therapeutic use of such violent substances as mercury, sulfur, and other chemicals. The fact that he escaped punishment gave courage to other independent thinkers in the field of medicine. It was also a part of the revival of the scientific spirit, a movement that stimulated the idea of research, the seeking for facts.

The reformation in medicine was, in part at least, a revolt against the teachings of Galen and the Arabian scholars. While

[1] HAGGARD. *Op. cit.*

many advances stimulated progress in surgery, the changes in other fields of medicine were negligible, with the exception of internal medicine, which was improved through the influence of Paracelsus. The progress made during the Renaissance paved the way for the advances that followed in the sixteenth and seventeenth centuries.

The Development of Pharmacy in Italy.—The duties of physicians and apothecaries in Venice were prescribed in a regulation in 1258. However, the profession of pharmacy and the apothecary shops existed long before there were laws enacted to regulate them. The drug trade, both wholesale and retail, was in the hands of the *speziarii* and *aromatarii*.

There were guild-like associations in ancient Rome founded for social, relief, military, and, possibly, educational purposes. During the Middle Ages in Italy, there were numerous guilds of merchants and craftsmen serving many purposes, chiefly political. In order to be a citizen, eligible for public office in certain cities, it was necessary to be a member of some guild. Many famous men, among them Dante, became members of the guild of physicians and apothecaries.

In the fourteenth century the number of apothecaries and wholesalers of drugs and spices was large. In 1349, one of the guild statutes mentioned 206 articles as being a monopoly of the guild of apothecaries or spicers.[1] From all accounts, membership in the guild of apothecaries had considerable significance. The shops were inspected at least once a year, and persons found guilty of selling substandard drugs were punished by being deprived of their right to practice their profession for a stated period of time. There was, of course, variation in the regulations pertaining to the profession of the apothecary from city to city in Italy and the other countries of Europe. One of the regulations, often mentioned, was that the apothecary was forbidden to give the physician a portion of the profits from the prescriptions written by the latter.

In Italy, pharmacy and the profession of the apothecary were held in high esteem previous to, during, and following the Middle Ages and the Renaissance. This has continued to the present time. In the Italian army of today, pharmacists hold com-

[1] KREMERS and URDANG. *Op. cit.*

missions, the lowest being that of second lieutenant and the highest that of a colonel.

The expanding Italian trade in drugs and spices stimulated the search for an all-water route to the Orient. This led to the discovery of America in 1492 and to the decline of Italian domination of the trade routes of the world, especially as pertained to drugs and spices.

A statute of the sixteenth century states that an apothecary was required to serve as an apprentice for 5 years and as clerk for 3 more years and then to pass an examination before being permitted to operate a shop of his own. Compare these requirements, which were in force for a long period, with those of the United States enacted a few decades ago. The number of pharmacies was limited to 1 for each 5,000 inhabitants in certain cities, although this ratio varied from city to city. All such restrictions in Italy were removed in 1888 to be reestablished in 1913. The standards for the practice of pharmacy in Italy have been high for centuries and continue to be so although the number of outstanding Italian pharmaceutical scientists is not great. In this respect, Italy cannot be compared with France or Germany.

Italy should be credited for many advances in European pharmacy. The "Ricettario fiorentino," the first pharmacopoeia of Europe, made its appearance in 1498. It was compiled by physicians with the help of pharmacists and was made official in Florence. The first botanical garden, the first institution to offer academic instruction in pharmacognosy, and the first professional apothecary shop were established in Italy. The records indicate that a series of city-state pharmacopoeias followed the appearance of the first one mentioned above. The first Italian pharmacopoeia was published in 1892.[1]

Pharmacy in France.—In France the guilds were professional organizations and were not of a political character as in Italy. In addition to self-regulation through the guilds, pharmacy was subject to both state and local authority. The first of the guilds appeared in 1270. In 1281 the apothecaries established a headquarters building in Dijon. In the fourteenth century the

[1] KREMERS and URDANG. *Op. cit.*

control of weights and balances was entrusted to the association of apothecaries and spicers. They disputed among themselves, and in 1484 the spicers were forbidden to practice pharmacy. It was recognized at that time that the compounder of prescriptions is a scientist and possesses a knowledge of drugs. While the spicers were no longer permitted to practice pharmacy, the apothecaries could still pursue the profession of the spicer and were later required to pass a spicer's examination. This brought the spicers and apothecaries together again for a time, but in 1777 when the guild of the apothecaries became the College of Pharmacy the separation of the two callings ended a quarrelsome union.

There were many guilds in France, and these made it possible for the profession to maintain high standards. Requirements for entrance to the profession were rigidly enforced. One apprentice was permitted for each pharmacy, and the number of shops was limited by statute or other means. The apprentice or his family was required to pay a considerable sum for the privilege of learning the profession. It was often a question as to whether the apprentice and his family would have enough money to purchase a pharmacy when the time arrived to open an establishment.

Apprentices had to pass difficult examinations in spite of the fact that the profession was often a family affair, *i.e.*, that sons or nephews followed their father's or uncle's business. The years of apprenticeship varied from 6 to 16 years.

The professions of medicine and pharmacy were at enmity for centuries in France. Nevertheless, pharmacy progressed and became a respected profession there. Academic studies were required of the apprentices of pharmacy, in addition to attendance at open lectures pertaining to the practice of pharmacy. In 1675 a chair of pharmaceutical chemistry was created at Montpellier. In the century that followed there were several famous pharmaceutical chemists in France, among whom were Rouelle and Baumé.

In 1797, a free school of pharmacy was set up in France. At the same time the first French journal of pharmacy appeared and was entitled *Journal de la Societé des Pharmaciens de Paris.* This was consolidated with *Annales de chimie* two years later.

Other journals of pharmacy and societies appeared later, among the latter being the Societé de pharmacie organized in 1803.

During these years the apothecary shops improved in appearance and became more attractive, often being decorated with beautiful pots and jars. French pharmaceutical chemists made many interesting and important discoveries in the early part of the nineteenth century. This did much to advance the sciences of pharmacy and plant chemistry.

A few of the important French scientists and their discoveries are given here. Derosne reported a *principium somniferum*, a mixture of morphine and narcotine, in opium in 1803; Sertürner (1783–1841) discovered morphine in 1806; Caventou (1795–1877) and Pelletier (1788–1842) together discovered strychnine in 1818 and quinine in 1820; Courtois found iodine in the ashes of seaweed in 1811; Balard (1802–1876) discovered bromine in 1826. These and many other famous French pharmacists owed their success to the training that they obtained in the practice of pharmacy.

The French produced a fine pharmaceutical literature in the form of textbooks, pharmacopoeias, and commentaries. The oldest pharmaceutical journal in the world still published is the *Bulletin de pharmacie*, first published in 1809. It is now called the *Journal de pharmacie et de chimie* and is both professional and scientific.

In France, as in Germany, there were many city pharmacopoeias, the most famous being those of Paris, Lille, Bordeaux, and Lyons. In addition, there were important and widely used pharmacopoeias written by famous French pharmacists. Among these should be mentioned the "Pharmacopée royale" by Charas, the "Pharmacopée universelle" by Lemery, and the "Eléments de pharmacie" by Baumé. The first French pharmacopoeia appeared in 1818 under the title "Codex medicamentarius seu pharmacopoeia Gallica." Its use was made obligatory for the whole of France, and it was adopted by many other countries of the world. It has gone through several revisions, the most recent being the sixth, in two volumes, issued in 1937.

Many French apothecaries have been among our most distinguished scientists. It is reported that 13 apothecaries were members of the French Academy prior to 1803, and a number are

now members of the French Academy of Medicine. French pharmacists have rendered distinguished service in the army in their professional capacity and attained the rank of *apothicaire-major général.*

French pharmacists have contributed much to the development of the pharmaceutical industry in their own country. The profession of pharmacy as a whole is greatly indebted to a long line of distinguished scientists, soldiers, writers, apothecaries, and statesmen who were Frenchmen.

Pharmacy in Germany.—The practice of pharmacy in Germany has always been regulated by the government and has never been self-governing as in Italy and France. During the Middle Ages apothecaries were too few to organize a guild of their own, but they often belonged to other guilds and were allowed to hold office. Germany granted them special privileges that gave them a monopoly of the sale and manufacture of drugs and medicinals and exclusive rights to practice pharmacy in specified cities. The right to open a new pharmacy was dependent upon a so-called "concession." This led to governmental control in the matter of opening new pharmacies and limited the number according to the population in a given district. In modern times, far from having a drugstore on every corner, Germany has had one pharmacy for about 8,000 persons. This means that pharmacy has been kept a profession in Germany. In some sections the pharmacy was handed down from father to son provided that the son met all the qualifications. In others the shop was neither hereditary nor transferable. In some German states the pharmacies were the property of the state and were operated by lease to pharmacists. State pharmacies were known in Germany as early as the thirteenth century.

The government, in granting concessions to pharmacists, expected them to serve the public welfare. Since it was not always possible to maintain a profitable business from the sale of drugs alone, certain goods such as spices, tobacco, and coffee were sold by pharmacies exclusively and were forbidden to be sold by the general trade. In time such monopolistic rights were more and more restricted to the sale of medicaments only.

In 1872, an imperial edict removed all unprepared and unmixed drugs from monopoly by pharmacists, excepting those which were

considered to be very potent. Cosmetics, dietetic materials, and prophylactics were also removed from the monopoly. This action led to the development of a distinct class of shops, known as *Drogerien*. The operators of these shops have wanted in recent years to be recognized as second-class pharmacists.

For several centuries in Germany those who sought to practice pharmacy have had to meet rigid educational and apprenticeship requirements. These were sufficiently high in the eighteenth century, and even later, to permit German apothecaries to be represented in the scientific professions. As universities grew, in order to qualify as a first-class pharmacist, the candidate was required to attend lectures at the university upon the subjects of chemistry, botany, pharmaceutical preparations, and related topics and to serve 7 years as a clerk, following an apprenticeship. Second-class pharmacists were not required to pursue such extensive studies but had to serve long periods of apprenticeship and clerkship and then pass an examination given by the local medical board.

The educational requirements, regulations concerning professional experience, and examinations for German pharmacists are still on a high level and, perhaps, are more exacting than those of other countries. First-class pharmacies are inspected by a medical officer. Second-class pharmacies are inspected by persons appointed within the profession.

The German apothecary is a representative of the middle class, usually well to do and respected. In times past, he was the scientist of his community. Apothecaries were not infrequently elected to the office of mayor, senator, or deputy. The German pharmacy is a place of dignity and distinction and represents culture that is lost to the American pharmacy.

Germany has given us the richest pharmaceutical literature in existence. Numerous city and state pharmacopoeias appeared in Germany following the publication of the "Pharmacopoeia Augustana" in 1564. This book listed about 1,100 medicinal agents. The "Pharmacopoeia Wirtenbergica" of 1741 contained 1,952 different medicaments and was reputed to be one of the best pharmacopoeias of its day. Most of the many German pharmacopoeias went through several editions, revisions, and changes. There were also many commentaries upon certain of

the pharmacopoeias. It was not until 1872, following the political unification of Germany, that the first pharmacopoeia of the empire appeared under the title "Pharmacopoeia Germanica." This text has been revised from time to time, the latest revision to date appearing in 1926. Good accounts of the pharmacopoeias of Germany and other countries as well are to be found in "Plantes officinales" by Bruntz and Jaloux (1918) and "Die Arzneibücher" by Falck (1920).

Thus pharmacy in Germany acquired the status of both a profession and a science. It gave expression to its progress and accomplishments through journals as well as through books. The first pharmaceutical journal was founded by Goettling in 1780. It was entitled *Almanach oder Taschenbuch für Scheidekuenstler und Apotheker.* Many other journals of pharmacy appeared in Germany within the next half century. One of the better ones, which has survived through various mergers and which dates back more than a century, is *Archiv der Pharmazie. Annalen der Chemie,* commonly referred to as *Liebig's Annalen,* was originally *Annalen der Pharmazie* and later carried the title *Annalen der Chemie und Pharmazie.* After Liebig's death the words *und Pharmazie* were dropped from the title. Many of these journals were organs of societies or associations. There were also several independent journals, devoted to the cause of pharmacy, which have come down to the present. Among them are *Pharmazeutische Zentralhalle* founded in 1859 and *Pharmazeutische Zeitung* founded in 1856.

"There has been scarcely one branch of natural science which has not been promoted very definitely by German pharmacists. The rapid development of scientific and industrial chemistry starting at the end of the eighteenth century is doubtless to a great extent due to the noble evolution of French and German pharmacists in just this field of science."[1]

Pharmacy in England.—During the latter part of the Middle Ages in England there were three classes interested in drugs, namely, those of the physicians, apothecaries, and drug merchants. In time, dissensions arose among these groups, and as a result there developd a fourth class, that of the pharmacists.

[1] KREMERS and URDANG. *Op. cit.*

It should be borne in mind that the pharmacists as a class gave us the Pharmaceutical Society of Great Britain (1841) and the American Pharmaceutical Association (1852) as we know them today.

Prior to 1511, anyone could practice medicine in England, and quacks of all kinds set themselves up as medical practitioners. Meanwhile, medical schools were established at Oxford and Cambridge, and these offered training for the reputable physician. In order that the bona fide physician might be distinguished from his quack competitor, the first Medical Act was passed in 1511. By this act only approved physicians could practice medicine within 7 miles of London. These accredited physicians founded the College of Physicians in 1518 and assumed the right to inspect the shops of the apothecaries, with the power to destroy drugs and preparations that were considered inferior or adulterated. In 1540, the practice of surgery was protected by law. It seems, however, that the surgeons abused the power granted to them, and in 1542 an act was passed that permitted anyone to practice medicine gratuitously. The apothecaries took advantage of this situation by making no charge for medical services but charged for the drugs and medicines that were considered necessary in treating the patient. Perhaps this was the beginning of the much-discussed problem of counter prescribing with which we still have to contend. In 1721, the apothecaries were granted the right to practice medicine on the same basis as physicians.

The apothecary, as early as 1290, supplied drugs and medicines to the royal households in England. Not only were the apothecaries subject to inspection by physicians, but they had guilds with which to contend. In early England the trade in drugs and spices was carried on by a class of merchants called mercers. In 1180, the Guild of Pepperers, which specialized in drugs, was organized. The apothecaries were associated with them but were not allowed professional status. In 1428, the Guild of Pepperers and the Guild of Spicers united to form the Company of Grocers, which was given official status by being granted a charter. The apothecaries were displeased with their lot, that of being associated with the grocers and subject to the discipline of the guild, and finally, in 1617, formed a separate guild known as

the Society of Apothecaries. Many studied surgery and medicine and became members of the Surgeons' Company. In 1815, the Apothecaries' Act granted the society the right to issue licenses to practice medicine in England and Wales and to control the practice. Thus arose the general practitioner of medicine and surgery.

The grocers and pepperers who had specialized in drugs prior to the organization of the Society of Apothecaries continued as druggists or dealers in drugs but were prohibited from keeping an apothecary's shop. In 1623, the Society of Apothecaries founded a dispensary for the purpose of making preparations for its own members. This part of the business expanded rapidly and became a source of supply for the drug-trade industry.

The fact that the apothecaries were granted the right to practice medicine gratuitously led to jealousy and disputes on the part of the younger physicians. In 1697 the physicians attached a dispensary to the College of Physicians, where prescriptions were dispensed at cost. This was in competition with the free medical service of the apothecaries and was sufficiently successful to lead to the opening of a second dispensary. The business of the apothecaries was so greatly reduced that they tried to reach an agreement with the physicians. The outcome was that the dispensing assistant appeared on the scene as supplier of drugs and medicines. He later became known as a *dispensing chemist*, a *chemist*, or a *pharmaceutical chemist* and is considered to be the predecessor of the present-day pharmacist.

During the sixteenth century there were many disputes among the apothecaries, physicians, and chemists and druggists. The position of the apothecaries became weaker, while that of the two latter groups became stronger. In the struggle the chemists and druggists had no association to do battle for them although they usually had the support of physicians. The apothecary had neglected pharmacy for the practice of medicine. The issue came to a crisis in 1841, and the Pharmaceutical Society of Great Britain was founded. Provision was made at once for the education and examination of chemists and druggists who sought to practice pharmacy. This was designed to place the pharmacists above reproach with respect to their qualifications to practice pharmacy.

If time and space permitted the review of the development of pharmacy in England up to 1841, it would be clear that the apothecaries aspired to become medical practitioners because of the odium which rested upon pharmacy as a trade. The apothecaries became medical attendants for their communities. In fact, they were medical practitioners and were not apothecaries in practice. Meanwhile, druggists and chemists grew in number and importance and gave rise to the founding of the Pharmaceutical Society of Great Britain, which became a corporate body in 1843 with power to regulate the education and admission of its members. Later, boards were set up to examine and grant certificates for those who qualified as pharmaceutical chemists. In time, all members of the profession were required to become registered. As time went on, there were many acts and amendments that gave increased power and authority to the society over affairs relating to pharmacy. The Pharmacy Act of 1933 has been called the Magna Charta of British pharmacy. This act made every registered pharmacist a member of the society.

While the practicing pharmacist in England and America can trace his lineage back through chemists, dispensing assistants, and drug merchants, "the medical practitioner of today is the lineal descendant of the apothecary of the seventeenth century."[1]

At the time of the organization of the Pharmaceutical Society of Great Britain, the *Pharmaceutical Journal* was founded and a School of Pharmacy established. In 1842, Prof. Redwood was appointed to the chair of pharmacy and filled this position with distinction until he resigned in 1885. Prior to this time, there were no facilities for pharmaceutical education except by apprenticeship. In the year following the first course of lectures at the college, a laboratory was set up for practical instruction in chemistry. The curriculum and the laboratory facilities were revised and improved from time to time to meet the demands made upon them. In 1900, laboratories were provided for pharmaceutical research. In 1925, research was extended to cover problems of biochemistry and pharmacology. The school is now known as the College of the Pharmaceutical Society of Great Britain and is a part of the College of London University.

[1] C. WALL. "The London Apothecaries, Their Society and Their Hall," Apothecary Hall, London, 1932.

The pharmacopoeias of Great Britain, which profoundly influenced the practice of medicine and pharmacy of the American colonies, were those of London, Edinburgh, and Dublin. The first edition of the "London Pharmacopoeia" appeared in 1618, the first "Edinburgh Pharmacopoeia" in 1699, and the first "Dublin Pharmacopoeia" in 1807. The first "British Pharmacopoeia" (B.P.) appeared in 1864, many years after the first "Pharmacopoeia of the United States of America" (1820). With the first "British Pharmacopoeia" there appeared the book "A Companion to the British Pharmacopoeia." This was a useful guide for physicians. Dispensatories also were published independent of any connection with the society, but these were not very popular, with one exception, namely, "Quincey's New English Dispensatory," which went through several editions. The latest revision of the "British Pharmacopoeia" appeared in 1932. Formularies that supplement it are the "British Pharmaceutical Codex" (B.P.C.) published by the authority of the Pharmaceutical Society of Great Britain and the "Extra Pharmacopoeia" (E.P.).

The number of scientists who have come from the ranks of pharmacy in Great Britain is not large. Prior to the founding of the Pharmaceutical Society the English apothecaries were practicing medicine. The great chemists of England were not pharmacists, as was the case in France and Germany.[1]

The wholesale and pharmaceutical manufacturing industries became well established in England. The story of the house of Allen and Hanburys is interestingly told in "Plough Court" (1927), a book issued by the house. A younger firm, that of Burroughs, Wellcome & Co., is at this time one of the largest in England and known all over the world. Henry Wellcome, one of the founders, was an American who became a naturalized Englishman.

Pharmacy in the United States.—Most of the physicians who came to America with the early settlers were from England. We have learned that in England the medical practitioners were often apothecaries who not only diagnosed and prescribed but often dispensed their own medicines. This custom had certain

[1] J. W. COOPER. "Initial Pharmacy," Sir Isaac Pitman & Sons, Ltd., London, 3d ed., 1941, Chap. I.

advantages in a pioneer world, for it was difficult to obtain the services of a physician in the early days in America except in the larger communities. Household remedies were widely used. There were persons who gathered and sold herbs, and others who could cup and bleed and perhaps also pull aching teeth. Preachers, who traveled on horseback to towns and villages, usually carried a limited supply of medicaments in their saddlebags and cared not only for the spiritual but for the physical needs of the people. Many of them were, in fact, physicians as well as ministers. There were midwives for confinements and much neighborly nursing in times of illness.

The early physicians in America, being also apothecaries, imported the needed medical supplies from London. There were apothecary shops with interesting signs, such as the Pestle and Mortar, Unicorn, and Dove. Many an early stock of medicine was supplemented with paints, glass, glue, and dried fruits.

As time went on, medicine and pharmacy became separated. The dispenser of drugs and medicine was called a pharmaceutist. Some time after 1870 the name was changed to pharmacist, the latter term being in wide use today.

National-group Influences in Early America.—While the early colonists along the eastern seaboard were dominantly English, there were other influences that made profound impressions upon the young nation. Spanish influence was marked in Florida, Texas, and California. The French were influential along the Saint Lawrence River, near the Great Lakes, in Illinois, and along the Mississippi as far south as Louisiana. The domination of the Dutch was confined to the New York City area. The Swedish prestige was felt in Delaware and that of the Germans in and near Philadelphia. If space were available, it would be interesting to enlarge upon the contributions to the development of pharmacy and medicine in the United States that each of the national groups made.

Medicine and Pharmacy of the Pioneers.—The pioneers of America had to endure the hardships of primitive conditions. This was especially true with respect to medical services. It had been stated that "medicine was promulgated for the first hundred years of colonial America, by three types of individuals:

the governors, the churchmen, and the educators."[1] Much in the way of medical care and nursing was left to the housewife. Even today every wife and mother serves as a sympathetic nurse and dietitian to the sick members of her household. However, she can get help and advice from many sources; this was not the case with those who pioneered.

The early settlers of America were, without doubt, a hardy group and were able to do without much in the way of service from doctors and pharmacists. The pioneer physician sometimes resorted to other occupations for a livelihood, doctors and pharmacists often being theologians. The itinerant preacher and missionary was frequently the physician-pharmacist, not only to the settlers, but to the Indians.

It was only natural that the medical practices of the New World should reflect those of the Old World. Thus there persisted much of the old European credulity and superstition concerning the action and use of drugs, reinforced by what was derived from the Indians. This has been dispelled all too slowly, some part of it affecting the mind of the public even today. Moreover, ignorance resulted in the adulteration of drugs used in medicines. Incapable of selecting drugs of quality, practitioners often chose inferior drugs because they were offered at lower prices. This was serious, in view of the fact that so much faith was placed in the efficacy of drugs as curative agents, and dangerous drugs were at times sold unintentionally.

Physicians in the early days in America usually had one or more apprentices serving them. They became proficient in the use of the mortar and pestle and experienced in the making of powders, extracts, tinctures, pills, and plasters. Every physician had an establishment where these useful medicinals were made and sometimes offered for sale.

The apprentices usually served the doctors, at rather poor pay, for 5 years or more and then established themselves as physicians, for those who practiced medicine were not subject to regulation or license. This lack of regulation and license both for medicine and pharmacy prevailed all too long in the United States. Medicine has become a strong, well-organized

[1] KREMERS and URDANG. *Op. cit.*

profession within the past forty years. Pharmacy, within the same period, has made appreciable gains but is still not a strong professional body compared with its sister professions of medicine, dentistry, and nursing.

The Separation of Pharmacy from Medicine.—The separation of the practice of pharmacy from that of medicine came about gradually and was not the result of an edict or a law on the part of the state. The first apothecary shops in America were the dispensaries of medical practitioners, and in these the men who intended to practice pharmacy only had to learn their profession. This situation persisted until a little over a century ago.

The man who is given most credit for effecting the separation of pharmacy from medicine in this country is Dr. John Morgan. He completed his medical education abroad, where he learned to know that the two professions could exist separately to the mutual benefit of both. He determined, as a physician, never to dispense medicines but to write prescriptions only. Upon his return to America he brought an English apothecary with him, by the name of Leighton, who set up a prescription shop in Philadelphia. It was well stocked with drugs from London and, so far as is known, was the first of its kind in America.

Dr. Morgan, as early as 1765, held the view that the business of pharmacy is essentially different from that of the physician and the surgeon and that no one man should be physician, surgeon, and apothecary. Morgan's contemporaries, however, did not approve of his opinions, and it was not until the end of the eighteenth century that the writing of prescriptions by physicians and the compounding of them by pharmacists became the accepted practice. Pharmacy in America is therefore not an old profession. This should inspire hope for better days to come and encourage us to elevate pharmacy to the level of a profession and maintain it independently as such.

The Oldest Pharmacies in the United States.—It may be of interest to list a few of the first pharmacies in the United States as taken from "Early History of Pharmacy in America."[1] They are as follows:

[1] O. RAUBENHEIMER. "Early History of Pharmacy in America," *Medical Life* **33** (No. 2) (February, 1926).

1729 Christopher Marshall, apothecary shop of the Golden Ball, Chestnut and 2d St., Philadelphia.
1752 First pharmacy in Bethlehem, Pa.
1786 Carl Heinrich Heinitch, Lancaster, Pa.
1791 W. L. Bond, Fredericksburg, Va., the oldest pharmacy in Virginia.
1792 Stabler-Leadbeater Pharmacy, Alexandria, Va.
1796 Frederick Miller, apothecary shop of the Golden Mortar, the first pharmacy in Washington, D. C.
1800 First pharmacy in Middletown, Conn.
1802 First pharmacy in Poughkeepsie, N.Y.
1806 Dr. J. Peck, first pharmacy in Burlington, Vt.

This is not a complete list but is offered to acquaint the student with the dates when the pharmacies, as we know them, became established in this country. The Stabler-Leadbeater Pharmacy at Alexandria, Va., has been restored and preserved as the property of the American Pharmaceutical Association and is an interesting historical landmark. The corner drugstore is a comparatively recent institution, one that owes its existence, perhaps, to the merchandising of a variety of commercial items made available to evening shoppers because of the late closing hours of the average pharmacy.

Pharmaceutical Education.—According to Kremers and Urdang,[1] the first course of lectures on theoretical and practical pharmacy was offered by James Cutbush in 1812. Four years later, Dr. James Mease, a Philadelphia physician, made an effort to give instruction to pharmacists, but without success. In those days, pharmacy was looked upon as an art to be learned by serving an apprenticeship to one skilled in the art, and there were no laws that required attendance at lectures on the subjects of pharmacy, chemistry, materia medica, etc.

In 1821, the Philadelphia College of Apothecaries was organized and at once became a teaching institution offering evening courses in chemistry, botany, and materia medica for the benefit of the apprentices in Philadelphia. There is evidence that this organization was initiated by a group of Philadelphia apothecaries who resented the action of the University of Pennsylvania by which it granted the honorary master of pharmacy degree to 16 apothecaries of the city. The University of Pennsylvania

[1] *Op. cit.*

had stipulated that the recipients of these degrees must have served 3 years as apprentices, attended two courses of lectures on the subjects of chemistry, materia medica, and pharmacy, and passed a satisfactory examination, but it is not clear that these requirements were adhered to strictly.

The apothecaries of Philadelphia proposed to educate its apprentices and grant degrees in pharmacy, independent of the medical department of the University of Pennsylvania. The latter institution discontinued the granting of degrees in pharmacy, and the College of Apothecaries established the first college of pharmacy. For many years this was known as the Philadelphia College of Pharmacy. Today it is known as the Philadelphia College of Pharmacy and Science.

In these early days the colleges of pharmacy had to depend on the medical profession for teachers. Physicians lectured on the subjects of botany, chemistry, materia medica, and pharmacy. Pharmacy was not a major subject of instruction until 1847, when William Procter, Jr., was elected to the chair of pharmacy of the Philadelphia College of Pharmacy. From this time on, the subject of pharmacy held a major position in the curriculums of colleges of pharmacy.

The Massachusetts College of Pharmacy was organized in 1823 but did not become a teaching institution until 1867. The New York College of Pharmacy was founded in 1829 and offered courses in pharmacy and related subjects from its inception but was inactive from 1857 to 1869. Tulane University opened a course in pharmacy in 1838 in connection with the medical department. The Maryland College of Pharmacy, also a teaching institution, was founded in 1840 but was inactive from 1847 to 1856. The Cincinnati College of Pharmacy was organized in 1850 and the Chicago College of Pharmacy in 1859. The latter was closed at the beginning of the Civil War, did not reopen until 1870, and was destroyed by fire in 1871. In 1864, the Saint Louis College of Pharmacy was organized.

During the years between 1821 and 1864, eight colleges of pharmacy had come into being. It was clear that the struggle to keep them alive would not be easy. They were associations or corporations of local pharmacists who had banded themselves together for professional protection and advancement, and teach-

ing was but one phase of the purpose for which they had been organized.

During these same years the country was rapidly settled as emigrants, in great numbers, migrated to points west of the Allegheny Mountains and the Mississippi and even on to California. Many states had come into the Union, and state governments were developing to the point of exercising greater local control. State legislatures began to pass laws that placed the practice of pharmacy in the hands of members of the profession. State pharmaceutical associations first came into being in 1867 and multiplied rapidly in number from then on. With the laws came the boards of pharmacy. These lines of progress are mentioned because they all had a marked influence on the development of pharmacy in the United States.

An innovation in pharmaceutical education was introduced at the University of Michigan in 1868, when a course in pharmacy was instituted to meet the need for better and more specific training for chemists and pharmacists. Only those who were apprenticed were admitted to the courses of lectures of the older colleges of pharmacy. Michigan admitted students and even graduated them as pharmacists without any such requirement. This policy was contrary to that of the so-called "old-line" colleges and was objected to by them. Furthermore, the first class of 23 was graduated at Michigan in 1869 with the degree of **pharmaceutical chemist.** There was much objection to this new degree, but it has survived through the years of American pharmacy to the present.

There are many interesting points to be noted about this, the first course in pharmacy, to be offered by a state university. It revolutionized the old idea that pharmaceutical education should be in the hands of an organization of apothecaries. The University of Michigan was no such organization; yet it dared to train men in pharmacy.

A strong feature of the new curriculum was that practical laboratory work was offered in prescription compounding and chemical analysis. Prior to this time, instruction in pharmacy was chiefly comprised of lectures, which were supplemented, in later years, by demonstrations. Other schools of pharmacy were quick to follow the lead of Michigan in offering

practical laboratory courses. In most schools such courses were at first made optional but later were required.

As state laws were passed, controlling in a measure the practice of pharmacy, the states in turn were obligated to provide suitable means of education for prospective pharmacists. Beginning in 1883, the number of state-supported schools of pharmacy grew rapidly, the greater number being in the Central States although such schools were to be found in the South and the Far Northwest. Significantly, state-supported schools of pharmacy did not appear in the East in competition with the established colleges. However, a few of the older schools have become affiliated with state-supported universities in recent years.

In reading the story of the progress of pharmacy one is impressed with the significant advances that were made during the last third of the nineteenth century. Following the Civil War the country grew and expanded in all lines of endeavor. Pharmacy, naturally, shared in this expansion.

Just what was happening to pharmacy may be summarized in Table I. Here, in alphabetical order, is a list of states. To the right appear the years in which these states (1) organized state pharmaceutical associations, (2) passed first laws pertaining to pharmacy, and (3) organized state-supported schools of pharmacy.

It will be observed that the formation of the state associations usually preceded the passage of a state pharmaceutical law, in some cases, by a good many years. A number of these associations were reorganized at later dates, a few of them more than once. In one or two cases, also, the first law was not an all-state law but was amended and became such at a later date. Almost without exception, the organization of a state school or college of pharmacy was preceded by the organization of the association and the passage of laws pertaining to pharmacy within the state.

National Organizations of Pharmacy.—The organization of state associations in the latter part of the nineteenth century was contemporaneous with the organization of a number of national associations whose interests were essentially pharmaceutical. The first of these organizations was the American Pharmaceutical Association, founded in 1852. This was an

TABLE 1.—DEVELOPMENT OF PHARMACY IN THE UNITED STATES, 1881–1915

Name of state	Organization of state associations	Passage of first state pharmacy laws	State schools of pharmacy organized
Alabama	1881	1861–1887	1895
Arizona	....	1903	
Arkansas	1883		
California	1869	1891	1872[1]
Colorado	1890	1887	1911
Connecticut	1876	1881	1925[1]
Delaware	1887	1883	
Florida	1887	1872	1923
Georgia	1875	1867	1901
Idaho	1887	1887	1920
Illinois	1880	1881	1859[1]
Indiana	1882	1899	1884
Iowa	1880	1880	1885
Kansas	1880	1885	1885
Kentucky	1877	1874–1888	
Louisiana	1882	1888	
Maine	1867	1877	1894[2]
Maryland	1882	1902	1841[1]
Massachusetts	1882	1885	
Michigan	1874	1885	1868
Minnesota	1883	1885	1892
Mississippi	1871	1892	1908
Missouri	1879	1881	
Montana	1891	1895	1897
Nebraska	1882	1887	1901
Nevada	1932	1901	
New Hampshire	1874	1875	
New Jersey	1870	1877	1892[1]
New Mexico	1893	1889	
New York	1879	1869	
North Carolina	1880	1881	1880
North Dakota	1885	1891	1901
Ohio	1879	1884	1885
Oklahoma	1890	1891	1895
Oregon	1890	1891	1898
Pennsylvania	1878	1887	
Rhode Island	1874	1871	
South Carolina[3]	1872	1876	1866 1881[1]
South Dakota	1886	1890	1888
Tennessee	1873	1893	1901
Texas	1879	1889	1893
Utah	1892	1894	
Vermont	1870	1894	
Virginia	1882	1886	1893[1]
Washington[3]	1890	1891	1894 1896
West Virginia	1870	1881	1914
Wisconsin	1880	1882	1883
Wyoming	1915	1886	

[1] State support came some time after organization.
[2] No longer in existence.
[3] Two state schools.

association of pharmacists who saw the necessity for an organization in order to bring about improvement in the quality of imported drugs. The United States had become the dumping ground for an inferior lot of medicinal materials, and the better druggists in and around New York City, the principal port of entry, deplored this state of affairs. They therefore called a meeting in New York in 1851 in an effort to find ways of stopping the entry of questionable drug items. It is of interest to note that our first national drug act was passed in 1848 for the purpose of correcting the import evils which were known to exist. Those entrusted with the enforcement of the act were negligent in the performance of their duty. This explains, in part at least, the reason for the action of the druggists in trying to find a way to better conditions.

During the New York meeting it was suggested that a national, rather than a district, organization should be formed. The suggestion was well received and arrangements were made for the calling of an organizational meeting in Philadelphia in 1852, and at this meeting the American Pharmaceutical Association was instituted.

The American Pharmaceutical Association has survived more than nine decades of American history, and its record is a good one. It is the only organization that can speak for pharmacy in a professional way, and its officers have done so on many occasions in recent years. The association has been housed at the American Institute of Pharmacy, at 2215 Constitution Ave., Washington, D.C., since 1934. The Institute is perhaps better known as the Headquarters Building. The building is small but is a credit to any profession. Because of the judicious policies of the Association, both it and the Institute are in good standing with the departments of government in Washington, which often turn to the permanent secretary for information concerning pharmaceutical matters. It is important for students in pharmacy to think in terms of the association that represents pharmacy as a profession and to appreciate the value of membership in such an organization. At present, scarcely 5 per cent of the pharmacists of the country belong to the American Pharmaceutical Association, while about 75 per cent of all physicians hold membership in the American Medical Association. We

shall be able to expect better progress in pharmacy when pharmacists become better organized.

It is not possible here to discuss, even briefly, any of the other national associations related to pharmacy. Instead, they will be listed in the order of the dates of their organization. This should impress the reader with the fact that the national movement in pharmacy that followed the Civil War was a very real one and is reflected in the increasing number of associations.

1870–1883	First Conference of Colleges of Pharmacy.
1876	National Wholesale Druggists' Association.
1881	The Proprietary Association of America.
1883	National Retail Druggists' Association.
1897	Association of American Dairy, Food, and Drug Officials.
1898	National Association of Retail Druggists.
1900	Conference of Pharmaceutical Faculties (the American Association of Colleges of Pharmacy).
1904	National Association of Boards of Pharmacy.
1908	American Association of Pharmaceutical Chemists (American Pharmaceutical Manufacturers' Association).
1910	National Retail Drug Clerks' Association.
1912	National Association of Manufacturers of Medicinal Products (American Drug Manufacturers' Association).
1913	National Drug Trade Conference.
1915	Federal Wholesale Druggists' Association.
1922	National Conference on Pharmaceutical Research.
1932	American Council on Pharmaceutical Education.

This list shows a multiplicity of national organizations, all of which are anchored to American pharmacy but none of which can speak as one voice for it. The National Drug Trade Conference is perhaps the nearest to a federation of all these associations that pharmacy can claim but it has not been able to do what needs to be done, in a national way, for pharmacy. The fact that many of these organizations are outgrowths of the American Pharmaceutical Association is indicative of the activity and influence of the parent organization.

STUDY QUESTIONS

1. Is it true that man's desire for health stimulates research? Explain your answer.

2. To what extent was magic a part of the medical practice of the ancients?

3. Explain the demoniac idea of disease.

4. What is the significance of the Hippocratic oath to the modern physician? What does it indicate with respect to the practice of medicine in ancient Greece?

5. Explain how Rome got on for 600 years without doctors. What does this fact reveal concerning the life and customs of the Romans?

6. What part did the Byzantines play in the history of ancient medicine?

7. Explain briefly the rise and influence of the Arabs in Asia, Africa, and Europe.

8. Were the Arabs good custodians of ancient learning? Were they inventive? Were they literate? Explain your answer.

9. Did Arabic culture and civilization meet with opposition in Europe?

10. Explain the purpose of the guilds in Italy, France, Germany, and England.

11. To what extent and how was the number of apothecaries limited in the several countries in Europe?

12. When did medicine become distinct from pharmacy in Italy?

13. Where and when was the apothecary allowed to practice medicine?

14. Were the physicians in early America also apothecaries? If so, when did the separation of the two professions occur?

15. When did formal education for pharmacists begin in America? How did it come about?

16. Name the first 10 early colleges of pharmacy in America, and indicate which were teaching institutions.

17. If colleges of pharmacy in early America were not teaching institutions, what were they?

18. When did pharmacy become a subject to be taught in colleges of pharmacy? When was laboratory instruction in pharmacy introduced into the curriculums?

19. What was the significance of the state pharmaceutical laws and of the organization of the boards of pharmacy during the latter part of the nineteenth century?

20. What is the significance of the many national organizations of pharmacy?

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CHAPTER II

ETHICAL PRINCIPLES FOR THE PROFESSION OF PHARMACY

> The skill of an apothecary is a much nicer and more delicate matter than that of any artificer whatever; and the trust which is reposed in him is of much greater importance.—Adam Smith.[1]

Definition of Pharmacy.—One of the oldest textbooks on American pharmacy offers the following definition of the profession, which in a large measure is basically true today: "Pharmacy is the science which treats of medicinal substances. It embraces not only a knowledge of medicines and the art of preparing and dispensing them but also their identification, selection, preservation, combination, analysis, and standardization."[2]

In the revised guidance leaflet No. 14 issued by the United States Department of the Interior, **pharmacy** is defined as

> . . . [the] science and art of preparing from crude vegetable, animal and mineral substances and chemicals, materials in suitable and convenient form for use as drugs; the compounding of drugs; the dispensing of drugs and medicines according to prescription; and their distribution in other ways . . . [; it] also embraces the collection, identification, preservation, analysis, and standardization of drugs and medicines; the synthesis of medicinal chemicals; the preparation of biological products. A knowledge of the physical, chemical, and biological sciences is, therefore, essential for the intelligent practice of pharmacy.[3]

On the basis of the above definitions, the modern concept of pharmacy may be described by the following statements: **Pharmacy** is the study and application of the sciences that deal with medicinal substances. Not only does it compre-

[1] "An Inquiry into the Nature and Causes of the Wealth of Nations."

[2] E. F. Cook and Charles H. LaWall. "Remington's Practice of Pharmacy," J. B. Lippincott Company, Philadelphia, 8th ed., 1936, p. 1.

[3] Reprinted by the American Pharmaceutical Association as revised in 1941.

hend an understanding of medicaments, but also it embodies the techniques necessary for the preparing and dispensing of these substances in **suitable form** and with due regard to their appearance, identification, selection, preservation, combination, standardization, and analysis and synthesis. It requires an insight into the basic laws, theories, principles, and applications of bacteriology, botany, chemistry, mathematics, pharmacology, pharmacognosy, physics, physiology, and zoology.

It can readily be seen that pharmacy as defined in the preceding paragraphs can and should be classified as a **profession.** This is the definite conclusion reached in the report of the Commonwealth Committee[1] after a 2-year study

". . . [since] the materials that the pharmacist deals with are in many cases so dangerous in their effects upon physical well-being and the problems that face him in handling these materials and his contacts with the public require so much intelligence—**if they are properly performed**—that it is absolutely essential for him to have a rather wide and intimate acquaintance with the **fundamental sciences** upon which the art depends; and since the distinction between the **trade** and **profession** lies essentially in the fact that the trade needs to know only the methods in order to be proficient while the profession needs to know (in addition) the **principles** upon which the methods depends.[2]

The beginner in the study of pharmacy, therefore, must have a clear understanding of (1) **the underlying principles of the profession,** (2) **the aims and purposes of the sciences considered fundamental to the study of pharmacy,** and (3) **the subjects dealing specially with the theories and methods involved in the practice of the profession.**

Official and Nonofficial Standards of the Profession.—As requisites of the profession the pharmacist should possess the **latest** editions of the "Pharmacopoeia of the United States of America" and its supplements (commonly designated as U.S.P. XII), the "National Formulary" (N.F. VII), "The Pharmaceutical Recipe Book" (R.B. III), "New and Nonofficial Remedies" (N.N.R.), and "Accepted Dental Remedies" (A.D.R.). These publications enable him to compound excellent prepa-

[1] "Basic Material for a Pharmaceutical Curriculum," McGraw-Hill Book Company, Inc., New York, 1927, p. 13.

[2] Boldfaced type by authors.

rations of established medicinal value and to distinguish ethical ones from the many products that are marketed purely for commercial gain.

The Pharmacopoeia and the National Formulary are authoritative sources of information that the pharmacist should consult freely concerning drugs, chemicals, and preparations and their composition, purity, tests for identification and impurities, methods of standardization, and average doses. Because of the services rendered by these two books in supplying standards for medicinal products they have served as legal standards since the enactment of the first Federal Food and Drugs Law (1906) and are recognized as having a definite legal authority, also, under the Federal Food, Drug, and Cosmetic Act of 1938.

"The Pharmaceutical Recipe Book," a reliable work published by the American Pharmaceutical Association, offers to the enterprising pharmacist interested in developing profitable professional side lines a large variety of tested formulas as well as other valuable information.

"New and Nonofficial Remedies," a publication revised annually by the Council on Pharmacy and Chemistry of the American Medical Association, presents standards for new drugs, chemicals, and their proprietary products that have been proved of clinical value but that are not necessarily official in the Pharmacopoeia and the National Formulary.

"Accepted Dental Remedies," also revised annually, is published by the Council on Dental Therapeutics of the American Dental Association and serves as a guide for the dentist in the choice of drugs for his daily practice.

Importance of Professional Publications.—Libby has stated that "very little advance in culture could be made, even by the greatest man of genius, if he were dependent for what knowledge he might acquire upon his own personal observations. Indeed, it might be said that exceptional mental ability involves a power to absorb the ideas of others, and even that the most original people are those who are able to borrow most freely."[1]

Therefore, in order to serve as an individual disseminator of information concerning public health and community matters

[1] M. G. MELLON. "Chemical Publications," McGraw-Hill Book Company, Inc., New York, 2d ed., 1940, p. 1.

and as a coworker of the physician and the dentist, the pharmacist should be a discerning reader and a diligent student of recent literature dealing with advances in preventive medicine and medication. To render this service with intelligence and confidence he should subscribe to several recognized scientific journals such as the *Journal of the American Pharmaceutical Association* (*J. Am. Pharm. Assoc.*), including the Scientific Edition and the Practical Pharmacy Edition, and the *Journal of the American Medical Association* (*J. Am. Med. Assoc.*). These publications contain reports of original investigations along pharmaceutical and medical lines, as well as those of committees' findings, and also abstracts of scientific information published in this country and abroad. The pharmacist should subscribe to at least one reliable trade journal and have his name placed on the mailing lists of reputable manufacturers of medicaments who issue regularly dignified and worth-while informative house organs or publications.

The Value of Libraries.—As a further aid to enable him to acquire knowledge and information of a reliable nature expeditiously, the pharmacist should be familiar with scientific and public libraries and should be able to use them efficiently and intelligently.

The Private Professional Library and Its Importance.—Scientific and public libraries are not always accessible to the pharmacist, particularly if he is in a small community. Therefore, in order to fulfill his duties in respect to public health as an authority on matters pertaining to hygiene and first aid and the control of insects, fungi, and parasites, and to enable him to perform his function as a dispenser of medicine with better comprehension, he should have in his personal library at least the minimum number of books to cover these fields sufficiently.

Any list of books submitted that might constitute such a library can be extended to cover the several fields of endeavor that the enterprising pharmacist might care to follow. The following is a minimum representative list of books that would cover these fields adequately (see Appendix I, pages 577 to 582 for a suggested list by author, title, publisher, etc.).[1]

[1] See also the booklet "The Professional Pharmacy," American Pharmaceutical Association, 1933, p. 7.

The latest edition of "The Dispensatory of the United States of America" (U.S.D.).

"Useful Drugs."

Gutman's "Modern Drug Encyclopedia and Therapeutic Guide" and the Supplements.

A book on perfumes and cosmetics.

A chemical formulary.

A recent textbook on general or inorganic chemistry.

A reliable modern work on organic chemistry.

An up-to-date book on pharmacology.

Reprints of the articles in the *Journal of the American Medical Association* under the heading The Pharmacopoeia and the Physician. First series of 24 completed in 1937. Second series began in the autumn of 1938.

A recent book on toxicology.

A pharmacognosy or materia medica textbook.

One or more reliable textbooks on general pharmacy.

A recognized work on dispensing pharmacy.

A handbook of tables dealing with chemistry and physics.

A work on insecticides, fungicides, rodenticides, and parasiticides.

A reliable book on cosmetic dermatology.

One or more texts on physiology and anatomy.

"Nostrums and Quackeries" and other publications of the American Medical Association dealing with such exposures in the field of proprietary preparations.

A text dealing with the application of arithmetic and algebra to pharmacy and with the problems of commercial transactions.

A treatise on bacteriology.

A work on the problems of public health.

A first-aid manual.

A treatise on veterinary medicine.

Government publications on specific subjects such as public health, sprays, and insecticides.

A reliable medical dictionary.

A chemical dictionary.

A modern dictionary.

Many in the preceding list are publications such as are purchased and used as textbooks in the various courses taken by the student of pharmacy as partial fulfillment of the requirements for the bachelor of science degree in pharmacy in a recognized school. It is to the advantage of the earnest student to abrogate the much too common practice of disposing of a worthwhile text because he feels he will have no further use for it during the remainder of his undergraduate training or afterward.

Minimum Equipment of the Pharmacy.—The pharmacist should provide his establishment with the necessary equipment to dispense prescriptions properly, compound preparations, and perform the various tasks that confront him as a highly trained individual. Listing of the minimum standard equipment is suggested in Appendix II, pages 583 to 584. Reference should be made to "The Commonwealth Report," pages 322 to 330; to *Drug Topics* **54** (No. 23), 31 (1938); **54** (No. 25), 22 (1938); **85** (No. 41), 22 (1941); and to the monograph "The Professional Pharmacy," American Pharmaceutical Association, 1933, pages 5 to 6, for a detailed study of equipment requirements.

Manufacture of Medicinal and Other Preparations in the Pharmacy.—If the pharmacist has been properly trained and possesses the necessary equipment to carry on his professional duties satisfactorily, he should feel qualified and consider it ethical and a sound and profitable business practice to manufacture the medicinals recognized in the "Pharmacopoeia of the United States of America" and "The National Formulary." They have been proved clinically to be valuable in medication or in general use in ethical medical practice and thus can replace many of the costly and even unsound proprietaries and advertised brands not so verified.

With the aid of handbooks such as "The Pharmaceutical Recipe Book" and other works containing tested formulas, he should feel capable of compounding improved professional products as side lines for the dental and veterinarian professions and for agriculturalists and gardeners. He should be able to manufacture stains, solutions, diagnostic agents, and testing and volumetric solutions for hospitals and laboratories, as well as harmless yet worth-while cosmetic products of various types.

Meritorious Products versus Worthless Preparations.—If the activities mentioned in the last two paragraphs are to be conducted ethically, the pharmacist should take pride in manufacturing meritorious products only rather than serving as the vendor of preparations that, as a result of his training, he knows to be basically worthless. He should avoid the motive of profit taking by having foremost in his mind the best interests of the public he is serving.

Other Professional Activities.—On the basis of his professional training, interests, and study along specialized lines, the pharmacist, if properly located, should feel qualified to perform for compensation analyses and examinations of a scientific character when the opportunity offers and the requests are of an ethical character.

Advanced Study.—Even though the pharmacist has, in most cases, completed a portion of his education in a reputable school of pharmacy, has supplemented this by fulfilling his experience requirements in a pharmacy, and has obtained a license as a fully registered operator of, or in, a pharmacy, he should not assume the complacent attitude that his education has been completed. He should realize that such an attitude leads rapidly and certainly toward stagnation as a professional man. Rather, he should continue his education by taking advantage of the postgraduate or extension courses, refresher programs, or pharmacists' clinics that are now being planned and offered by progressive schools of pharmacy, provided that such courses are not for the most part too commercial in intention. Such courses are designed to acquaint the pharmacist by means of round-table discussions and instructions and lectures presented by recognized workers in specialized fields with the recent advances in, and trends of, the profession, thus modernizing his viewpoint and knowledge. Also, he should so arrange his hours as to enable him to continue his study by reading the various journals and publications mentioned previously.

Professional Research and Investigations.—The pharmacist should show an interest in, and devote a portion of his time and ability to, professional research and investigation. Several pharmacologists of note have come to the conclusion that it is the duty of a certain number of pharmacists, especially those with advanced training in pharmacy, pharmaceutical chemistry, or other branches of the profession, to devote their efforts toward the development of new medicaments for the benefit of mankind. These endeavors may be carried out in private laboratories or in universities, as well as in the laboratories of manufacturers of pharmaceuticals. Qualified students in schools of pharmacy would do well to consider preparing themselves for lines of private enterprise by continuing graduate work, with its advanced

instruction in specialized fields of research and study. Such examples of scientific initiative should receive the support and encouragement of the entire profession.

Professional Pride.—Above all personal attributes it is imperative that the pharmacist should develop within himself a professional morale **evidenced by a pride in his profession.** A just professional pride aids in developing character and personality, enabling the pharmacist to deal with people efficiently and confidently and to live and associate with them agreeably. His pride of profession should be on so high a plane that he will feel no inferiority in his relationship with other professional men. Similarly, he will never undersell his services, enter into unfair competition, or in any other manner render poor service to the public.

The Prescription as a Confidential Order of the Physician.—The pharmacist, as a professional man, should keep in mind that the prescription is the confidential order of the physician to the pharmacist and that its contents or action should never be discussed with the patient presenting it. The following incident quoted from a medical journal[1] illustrates the results of a violation of this trust: "A doctor gave a patient a prescription for sulfanilamide and when read by the pharmacist before the patient he pursed his lips saying: 'Mighty dangerous stuff, but I guess the doctor knows what he is doing.' The patient immediately called the doctor's office highly excited and it was some time before she could be reassured." Another instance from the same journal of a pseudo-physician-druggist making unnecessary comments on drugs ordered by the doctor is that of a pharmacist in a cut-rate drugstore who told the patient that the amount of codeine in the prescription seemed "pretty large."

Such incidents constitute direct violations of the principle of professional confidence. The significance of this relationship between the physician and the pharmacist for the welfare of the public is well illustrated by the timeless quotation from Spencer Percival: "The amicable intercourse and cooperation of the physician and apothecary, if conducted with decorum and attention to etiquette, which should always be steadily observed

[1] *Med. Economics* **15, 33–4, (1938).**

by professional men, will add to the authority of the one, the respectability of the other, and to the usefulness of both."

Obligations as a Man.—As a man, the pharmacist has certain obligations to his country, his family, and himself. In order to fulfill these he should be more than a competent technician. In addition to the topics mentioned in the preceding and following paragraphs, he should be interested in matters that may be classified as extravocational activities and duties. These include the developing of such qualities of an upright citizen as intelligence, forcefulness, reliability, physical and mental fitness and alertness, and enjoyment of life, art, religion, hobbies, etc. To ensure a better appreciation of these interests the modern pharmaceutical curriculum allows for some selection of the cultural subjects as required and elective courses.

The Public Servant.—As a public servant, the pharmacist should be especially interested in performing the duties that have to do with public health. As has been previously indicated, he, of all professional men, is the most strategically situated to give personal advice upon problems pertaining to public health and hygiene. He should be capable of administering first aid. He is obligated to assume an active part in all efforts to raise the standards of health and living in his community. He should therefore have a fund of knowledge relating to communicable diseases, not for the purpose of unethical counter prescribing, but to assist in all health movements directed toward the eradication of such disorders.

Knowledge of Professional Appliances.—In order that he may serve more effectively the various professions and the laity, with proper remuneration for himself, the pharmacist should have a thorough understanding of the many worth-while appliances that are marketed. These include devices for administering hot and cold applications, for irrigation, for hypodermic and allied forms of injection, and for protective purposes, feeding apparatus, thermometers, bandages and dressing materials, plasters, ligatures and sutures, hygienic appliances, bedpans, urinals, pus basins, inhalers, atomizers, eyecups, medicine droppers, glasses and spoons, breast pumps, nipple shields, and drip apparatus.

Laws Pertaining to the Profession of Pharmacy.—As a vocation, pharmacy is regulated by law to an unusual degree. It should therefore be the duty of the pharmacist to familiarize himself with the Federal, state, and local laws pertaining to his profession, especially those regulating the sale and manufacture of narcotics, spirituous liquors, poisons, hypnotics, insecticides, etc. He should respect also the honor of the profession and his reputation by refusing to adopt questionable practices that are just within the law for the purpose of selfish gains.

He should be aware of any form of proposed local, state, and Federal legislation that jeopardizes the standards of the profession or that imposes unfair tax burdens or onerous responsibilities upon pharmacy and should oppose all such acts. He should always support, vigorously, legislation that will raise the standards of the profession or improve the conditions of public health.

Professional Organizations.—The pharmacist should have an interest in, and be a member of, organizations promoting the welfare of the profession nationally and in the state and locality in which he lives. These include the American Pharmaceutical Association, the National Association of Retail Druggists, his state pharmaceutical association, and local drug clubs or guilds. He should lend active support to these organizations by attending their meetings whenever possible, should take part in the discussions at such meetings, and above all should lend wholehearted support and approval and financial aid to all endeavors—scientific, legislative, etc.—of these bodies that are undertaken for the advancement of the profession. As a citizen of a locality, he should be active in civic organizations and improvements that have as their primary purpose the upbuilding of a finer, healthier, and happier community.

The Pharmacist and His Competitors.—The pharmacist should develop an attitude of helpfulness and comradeship toward his colleagues in his community. Such an attitude should alleviate petty jealousies and animosities retarding the profession in a particular locality to the detriment of public welfare and pharmacy in general. Also, such cooperation should remove obstacles to the establishment of rotational schedules for opening and

closing hours. Shorter and rotational work schedules permit a proprietor and his assistants greater leisure. In this way, the public is assured better service because of the increased opportunity afforded the pharmacist for study, personal improvement, and relaxation.

Candidates for Pharmacy.—The pharmacist should be in readiness to encourage the youth of the highest character and ability to enter the study and practice of pharmacy.

The Pharmacist and His Employees.—As a proprietor or employer, the pharmacist should recognize the rights and privileges of his employees, especially those who have the same professional attainments that he possesses. Such employees have a right to his respect and confidence and the degree of enjoyable living that he tries to maintain for himself. The proprietor should recognize the fact that an employee happy in his working surroundings is one who is not underpaid or worn to exhaustion by long working hours but who is allowed leisure to enjoy life and improve himself professionally and socially.

The Employee.—The pharmacist as an employee should recognize the rights of his employer, and particularly so if he, also, is a pharmacist. The employer has a right to demand honesty, diligence, good habits, personal pride in dress and manners, loyalty, and unquestionable ethics on the part of the employee.

Meeting the Physician.—The pharmacist should be so familiar with the standards and official medicaments of his calling that he can detail and meet with the physician in mutual interest and consultation, to familiarize him with the most economical means of prescribing for the patient, in whose welfare they both should be primarily concerned.

Nonprofessional Commercial Pursuits.—To avoid the ever-present danger of overcommercialism that threatens the profession, the pharmacist should be careful not to promote nonprofessional commercial interests at the expense of his legitimate professional interests. The former interests have proved to be unstable and highly competitive and even unprofitable.

Professional Pharmacy and Commercial Pharmacy.—The pharmacist should not allow the terms *professional pharmacy* and *commercial pharmacy* to become confused in his mind and his

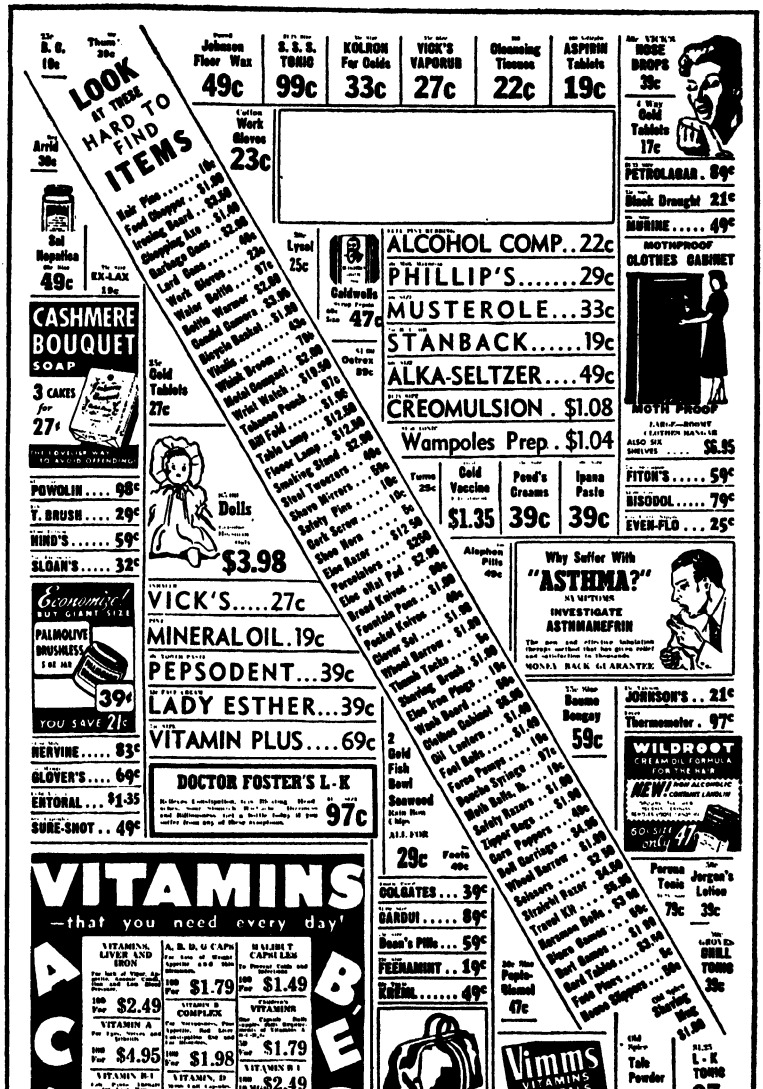

Plate 1.—Overcommercialism in pharmacy. A type of advertisement used by some pharmacies in daily papers of this country. Of more than 140 items listed in this advertisement, approximately 30 per cent are side lines that are either distinctly not legitimate or only remotely ethical.

practice. "The Commonwealth Report"[1] recognizes that the pharmacist, in the practice of his profession, "has to manage his business, to buy and sell, to advertise and display his merchandise, and to obtain profits sufficient to maintain his business and to secure the necessities, the comforts, and some of the luxuries of life." This permits the sale of legitimate side lines, which include the ever-increasing number of worth-while mechanical appliances, rubber goods of all description, thermometers, sick-room supplies, first-aid kits, infants' and health foods, cosmetics and perfumes, insecticides and fungicides, and allows the making of stains and diagnostic reagents and analytical and microscopic examinations. Commodities that rightfully belong in restaurants, grocery and department stores, meat markets, garages, etc., should not be sold (see Plate 1). To do so opens up fields of extraordinary and uncalled-for competition, which is a detriment to the profession and a source of anxiety to the professional man and of evils that cannot be remedied by any type of legislation in the form of fair-trade acts and acts controlling unfair competition.

Expanding into trade competition usually operates adversely, to harass not only other businesses but also the pharmacist himself whose field has been thus expanded. Unfortunately, many pharmacists of recent years have infringed on the sales scope of other businesses. Moreover, they have become "fence straddlers" in that they selfishly desire to be recognized as professional men with all the rights and privileges of this select group and yet wish to be protected from unfair competition and from inconveniences caused by trades of various types on whose fields of activity they have trespassed.

Loyalty to the Profession.—It is clear that the pharmacist should possess sufficient pride and satisfaction in the practice of his profession so that, under no circumstances, would he become a depreciator of pharmacy, which furnishes him his livelihood and is perhaps the only vocation he is capable of following successfully. He should always stand ready to support and promote vigorously the calling, thus obtaining from others a respect for it that is unqualified.

[1] "Basic Material for a Pharmaceutical Curriculum," McGraw-Hill Book Company, Inc., New York, 1927, p. 4.

Observance of Codes of Ethics.—If the pharmacist attempts sincerely to follow the principles set forth in the preceding pages, he will have little difficulty and take much pride in living up to a **code of ethics,** which most professions entrusted with the health and welfare of the public have developed. Since codes of ethics are indispensable in the maintenance of professional standards, a brief historical development, as well as the code of the American Pharmaceutical Association and a portion of that of the American Medical Association, is offered in the following paragraphs.

LaWall[1] says of the earliest of all codes, namely, the Hippocratic oath, that it is " . . . an example of idealistic precept which has never been surpassed, and which, as the common heritage of medicine and pharmacy, serves as the starting point for all codes of ethics, however modern they may be."

The oath follows in full.

I swear by Apollo the physician and Aesculapius and Hygeia, and Panacea, and all the gods and goddesses—and I make them my judges—that this, mine oath, I will fulfill as far as power and discernment shall be mine.

Him who taught me this art I will esteem even as I do my parents; he shall partake of my livelihood, and, if in want, shall share my goods. I will regard his issue as my brothers and will teach them this art without fee or written engagements if they shall wish to learn it.

I will give instruction by precept, by discourse, and in all other ways to my own sons, and to those of him who taught me, to disciples bound by written engagements and sworn according to medical law, and to no other person. So far as power and discernment shall be mine, I will carry out regimen for the benefit of the sick and will keep them from harm and wrong. To none will I give a deadly drug, even if solicited, nor offer counsel to such an end; likewise to no woman will I give a destructive suppository; but guiltless and hallowed will I keep my life and mine art. I will cut no one whatever for the stone, but will give way to those who work at this practice.

Into whatsoever houses I shall enter, I shall go for the benefit of the sick, holding aloof from all voluntary wrong and corruption, including venereal acts upon the bodies of females and males, whether free or slaves. Whatsoever in my practice or not in my practice I shall see

[1] CHARLES H. LAWALL. "Four Thousand Years of Pharmacy," J. B. Lippincott Company, Philadelphia, 1927, pp. 42–44.

or hear amid the lives of men which ought not be noised abroad as to this I will keep silence, holding such things unfitting to be spoken.

And now if I shall fulfill this oath and break it not, may the fruits of life and the art be mine, may I be honored of all men for all time; the opposite if I shall transgress or be foresworn. [See Plate 2.]

A similar manifest was proposed by Maimonides, a Spanish physician, in his oath and prayer (twelfth century).

Plate 2.—The Hippocratic oath. (*Courtesy of Arlington Chemical Company, Yonkers, N. Y.*)

In the fourteenth century, French apothecaries were required to swear to a formal oath before being permitted to practice.

They swore to live and die in the Christian faith, to speak no evil of their teachers or masters, to do all in their power for the honor, glory, ornament, and majesty of medicine, to give no remedy or purge without the authority of a physician, to supply no drugs to procure abortion, to prepare physicians' prescriptions exactly, neither adding, subtracting, nor substituting anything without the express permission of the physi-

cian, to avoid the practices of charlatans as they would the plague, and to keep no bad nor old drugs in their stocks.[1]

In 1848, the Philadelphia College of Pharmacy, the oldest college of pharmacy in the United States, adopted the first comprehensive code of pharmaceutical ethics, which is quoted in part.

Pharmacy being a profession which demands knowledge, skill, and integrity on the part of those engaged in it, and being associated with the medical profession in the responsible duties of preserving the public health, and dispensing the useful though often dangerous agents adapted to the cure of disease, its members should be united on some general principles to be observed in their several relations to each other, to the medical profession, and to the public.

We in like manner consider that an apothecary being engaged in furthering the interests of any particular physician, to the prejudice of other reputable members of the medical profession, or allowing any physician a percentage or commission on his prescriptions, as unjust toward the profession and injurious to the public.

As the practice of pharmacy can only become uniform, by an open and candid intercourse being kept up between apothecaries, which will lead them to discountenance the use of secret formulae, and promote the general use and knowledge of good practice, and as this college considers that any discovery which is useful in alleviating human suffering, or in restoring the diseased to health, should be made public for the good of humanity and the general advancement of the healing art—no member of this college should originate or prepare a medicine, the composition of which is concealed from the other members, or from regular physicians.

They earnestly recommend the propriety of discouraging . . . [the] employment [of secret and quack medicines], when called upon for an opinion as to their merits.

The apothecary should be remunerated by the public for his knowledge and skill, and his charges should be regulated by the time consumed in preparation, as well as by the value of the article sold; although location and other circumstances necessarily affect the rate of charges at different establishments, no apothecary should intentionally undersell his neighbors with a view to his injury.

As the apothecary should be able to distinguish between good and bad drugs, in most cases, as the substitution of a weak or inert drug

[1] *Ibid.*, p. 166.

for an active one may, negatively, be productive of serious consequences—we hold that the intentional sale of impure drugs or medicines, from motives of competition, or desire of gain, when pure articles of the same kind may be obtained, is highly culpable, and that it is the duty of every honest apothecary or druggist to expose such fraudulent acts as may come to his knowledge. . . .

As there are many powerful substances that rank as poisons, which are constantly kept by apothecaries, and prescribed by physicians, and which are only safe in their hands . . . we hold that the apothecary is not justified in vending these powerful agents indiscriminately to persons unqualified to administer them, and that a prescription should always be required, except in those cases when the poisons are intended for the destruction of animals or vermin—and in these instances only with the guarantee of a responsible person. And we hold that when there is good reason to believe that the purchaser is habitually using opiates or stimulants to excess, every conscientious apothecary should discourage such practice.[1]

Immediately after the founding of the American Pharmaceutical Association (1852), the organization formulated a code of ethics.[2] It has been replaced by a new code that more nearly answers the needs of the development of pharmacy in the present century. This was adopted in August, 1922, and has since been recognized by the National Association of Retail Druggists, the Canadian Pharmaceutical Association, and similar organizations in several of the South American republics.

This code is printed in full.

CODE OF ETHICS OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

(Adopted August 17, 1922)

CHAPTER I

THE DUTIES OF THE PHARMACIST IN CONNECTION WITH HIS SERVICES TO THE PUBLIC

Pharmacy has for its primary object the service which it can render to the public in safeguarding the handling, sale, compounding and dispensing of medicinal substances.[3]

[1] *Ibid.*, pp. 491–495.

[2] *Ibid.*, pp. 498–501.

[3] Boldface type by authors.

3. Give a list of preparations that the pharmacist is capable of making.

4. When should the education of a pharmacist cease?

5. How may the feeling of confidence in his profession be developed by the pharmacist in action and practice?

6. Enumerate the duties of the pharmacist as a public servant.

7. Why should the pharmacist have a knowledge of professional appliances?

8. How may cooperation be obtained by fellow pharmacists in a given community?

9. What factors that must be eliminated are adversely affecting the practice of pharmacy as a profession?

10. Define or explain what is meant by a code of ethics.

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CHAPTER III

THE PHARMACEUTICAL CURRICULUM

PART I. THE BASIC SCIENCES

What you can do, or dream you can, begin it.
Boldness has genius, power, and magic in it.

—Goethe.

The principles discussed in Chap. II are more clearly understood by the student of pharmacy if he has a definite conception of the purposes of the various courses that constitute the modern pharmaceutical curriculum. Furthermore, if he understands the content of these courses, it will be all the easier for him to appreciate the true objectives of the curriculums offered by the colleges or schools of pharmacy for the development of a **reliable, intelligent, and cultured pharmacist possessing a real pride in the profession** that he has chosen.

In the definition of pharmacy previously presented (page 44) it was stated that it is a study of the application of the sciences. Science, defined in a general way, is the organization and classification of the knowledge pertaining expressly to nature. It is so broad in its scope that no one person has the ability and the time to master all the matter relating to it. For this reason, science has been classified or separated into various divisions.

The observant individual interested in life and the world about him is naturally concerned with the various branches of science. The student of pharmacy, in particular, should possess an aptitude or develop a special interest in the basic sciences that are part of our curriculum. If he does not possess this aptitude or interest, the course of study may prove highly difficult.

The basic sciences include the **biological sciences** and the **physical sciences.** A discussion of these subjects follows.

Biological Sciences.—Biology is the science pertaining to life and the character, growth, and reproduction of living things.

It includes **botany,** which is a study of the plant kingdom, and **zoology,** a study of the animal kingdom. Many schools offer these subjects as separate courses. Others combine them in a course in biology. It is not the purpose of this work to discuss the merits of either mode of presentation, although there is much to be said in favor of either.

Botany, as outlined for a pharmaceutical curriculum, has two purposes, academic and practical. It deals specifically with the general characteristics and nomenclature (system of names) of plants, the structure, physiology, and contents of the living plant cell, life histories, cell walls, tissues, and organs and their functions. It is a basic science for the study of **pharmacognosy,** which will be discussed later. A knowledge of botany is necessary to the pharmacist in the identification of plant parts, especially those recognized in the Pharmacopoeia and the National Formulary.[1]

Zoology is a cultural study as well as a fundamental science for the study of physiology and other subjects having to do with the human body. It is concerned with the material bases of life, including the living cell, function and form in animals, and the classifying, heredity, evolution, ecology, and distribution of animals.

Physiology (human physiology) is the study of the physical and chemical regulation of the processes of human life. A knowledge of the normal functioning of the human body is essential to the student of pharmacy. He should understand the actions of the body mechanism if for no other reason than that such information may enable him to maintain his own health. Moreover, he can thus comprehend the action of the drugs that he dispenses.

Physiology is closely related to, and dependent upon, **zoology, chemistry,** and **physics;** to some extent, **pathology** and **psychology** are helpful adjuncts. The subject may be divided into **general physiology,** a study of the general laws of life and functional activity, and **systematic physiology,** which is a specific study of function according to the anatomical system. Protoplasm and the cell, including specialized ones, the blood and circulation,

[1] "Basic Material for a Pharmaceutical Curriculum," McGraw-Hill Book Company, Inc., New York, 1927, pp. 123–135.

CHAPTER IV

THE PHARMACEUTICAL CURRICULUM

PART II. THE PROFESSIONAL AND APPLIED PROFESSIONAL SUBJECTS

Knowledge is of two kinds. We know a subject ourselves, or we know where we can find information upon it.—Samuel Johnson.

The student of pharmacy, having acquired a suitable knowledge of the essentials of the fundamental sciences (Chap. III), is qualified to pursue the so-called "professional" and "applied professional subjects" of a more advanced character. **Professional courses** are those courses on advanced material which are necessary for the development of a fitting background for the practice of the **profession of pharmacy.** The term **applied professional courses** might be used to designate those basic and professional phases which are offered with special emphasis on their **essential applications to pharmacy.** For example, any basic course in chemistry might be taught as an applied professional course in **pharmaceutical chemistry,** using, wherever feasible, illustrations from the practice of pharmacy to emphasize a basic principle, theory, process, or application. Such courses should be offered in the school of pharmacy by qualified instructors trained in the particular branch being taught.

Required Professional Pharmaceutical Courses.—Pharmacy has been defined in Chap. II (pages 44 to 45). On the basis of this definition, it may be subdivided according to course content. An examination of these subdivisions indicates that they should be offered in logical sequence, in the order of their complexity and importance, throughout the curriculum, as a mental grasp of the fundamental courses is acquired. This continuity is indispensable in stimulating and maintaining the proper interest in and assimilation of the subject matter.

An elementary course with a content such as that of this text should be offered as an introduction to the study and pursuit

of the profession of pharmacy. The terms **fundamental principles and processes of pharmacy, beginning pharmacy, fundamental pharmacy, introductory pharmacy, fundamentals and operations of pharmacy, elementary theory of pharmacy, pharmaceutical technique,** etc., have been used to designate such a course.

Included in it should be the principles that are the foundation of pharmacy, a brief historical development, and the bases of professional morale and ethics. It should acquaint the student with those theories, calculations, and processes which have direct application to pharmacy. It should also include the background material of pharmaceutical history, literature, and terminology and the practical application of mathematics and physics to pharmacy. Accompanying laboratory practice is needful, with the object of training students in the primary operations of pharmacy. This course should be offered in the first year of study.[1]

Pharmaceutical calculations (pharmaceutical arithmetic, or pharmaceutical mathematics) is the application of mathematical calculations to all processes and procedures in the manufacture and testing of drugs. It also involves the rudiments needed by the pharmacist in compounding and dispensing prescriptions, in calculating costs, in conducting the processes of pharmacy, in assaying and preserving pharmaceutical products, and in reading intelligently the Pharmacopoeia and the National Formulary and similar works. The student should have a working knowledge of this subject in the study of the basic courses discussed in Chap. III. The pharmacist needs a very high degree of skill in the use of mathematical operations in compounding and preparing medicinals. The lack of this skill is a crucial matter, for deaths might result from toxic doses of medicaments, due to inaccurate calculations and measurements in the manufacture of a prescription.[2]

The importance of the content of this course should not be minimized; but if the student comes to the school of pharmacy with a qualified mathematical training in the secondary schools

[1] "Basic Material for a Pharmaceutical Curriculum," McGraw-Hill Book Company, Inc., New York, 1927, pp. 99–105.

[2] *Ibid.*, pp. 40–44.

and high schools, much of the material, being of a review character, might easily be refreshed and supplemented in all the courses offered in the pharmaceutical curriculum, rather than establishing a separate course. However, if it is offered, its elementary nature would logically indicate that it should be studied in the first year.

Pharmaceutical Latin is the Latin that pertains to pharmacy. It is offered so that the student of pharmacy may develop ease in using the scientific names of drugs and the ability to read, with accuracy, prescriptions written in this language. The pharmacist has less need for profound learning in Latin than for facility in deciphering prescriptions written in a variety of ways.[1] Like that of pharmaceutical calculations, the content of this course is of such an elementary nature that it may be satisfactorily offered as part of the various courses in pharmacy rather than as a separate subject. In the latter event it, also, should be studied in the first year.

Pharmaceutical jurisprudence (or pharmaceutical law) involves the study of the laws and regulations relating to the practice of pharmacy and a consideration of the principles of common law bearing upon the work and duties of the pharmacist. The course should be developed so that the student learns with exactness the salient points of these laws and regulations in order to avoid unintentional violations. This course most logically should be offered in the fourth year.[2]

History of pharmacy should be taught as a major means of developing professional morale and *esprit de corps* and should include a description of the origins, evolution, present status, and future possibilities of the profession. Outstanding pharmacists and their contributions to the art of healing should be discussed. A background for the development of professional ethics may be built up. The course should be so conducted that the student will take as much part in the assignments as the instructor, through preparing short topics and writing term reports on the significant features of pharmacy.

In conjunction with the **history of pharmacy**, a systemized study of the **literature of pharmacy**—past and present—is

[1] *Ibid.*, pp. 44–59.
[2] *Ibid.*, pp. 31–40.

desirable. With the rapid progress being made in pharmacy and allied professions and because of the pharmacist's strategic position as a source of information to the public, it is imperative that the student and the pharmacist know the basic material and current literature pertaining to his profession, the latter to include trade and scientific journals and books in many related fields. The student should become familiar with the literature available in the departmental and general libraries of the school or college he is attending; he should learn where and how to find information and be capable of analyzing the literature, when found, and of preparing reports, abstracts, reviews, and theses. The **history and literature of pharmacy** should be stressed early in the curriculum but as an organized course should most logically be offered in the third year.[1]

Pharmaceutical ethics and codes have been discussed in Chap. II. It is impossible to present this important aspect of the pharmacist's training in any one course. A code of ethics should be stressed and observed throughout the 4-year curriculum and subsequently should be conscientiously adhered to by the practicing pharmacist. It is only through such observance that professional morale and prestige can be raised and maintained at a high level.

A course in **pharmaceutical preparations** (galenical pharmacy; operative pharmacy) covers various classes of preparations—official and nonofficial—their manufacture, stability, and preservation, and the evaluation of the different forms and combinations of the medicinal substances involved. It is a prerequisite for **dispensing pharmacy** and should be allotted ample time in the second and/or third years to permit the development of a high degree of aptitude in the techniques of the operations involved in the manufacture of these products, their classification, and their composition. This course, therefore, presupposes a thorough training in the basic sciences, in the processes and calculations of pharmacy, and in pharmacognosy, etc.[2]

Advanced pharmacy (the pharmacy of inorganic and organic chemical substances and compounds of vegetable and animal origin; inorganic and organic pharmacy) is a pharmaceutical

[1] *Ibid.*, pp. 95–99.
[2] *Ibid.*, pp. 59–87.

study of the inorganic and organic chemical substances—official and nonofficial—used as medicines or in the manufacture of medicaments or employed for closely related purposes. Laboratory work consists in the manufacture of examples involving these substances. Application is made of the elementary material learned in general chemistry and inorganic pharmaceutical chemistry, organic chemistry and organic pharmaceutical chemistry, other basic chemistry courses, and the fundamental biological sciences. Its aim is primarily to familiarize the student with the main theories and facts associated with the preparation of the inorganic and organic substances specifically and in medicines in the Pharmacopoeia and the National Formulary, particularly all products in these involving chemical reactions, and to develop further aptitude in laboratory work. With the increasing development of new organic therapeutic agents, the content should be of such a nature as to acquaint the student with the pharmaceutical facts concerning, and uses of, the nonofficial products of proved clinical value as well as of the official ones. This course should be offered in the third or fourth year of the curriculum.

Dispensing pharmacy (dispensing; prescription compounding) is the application of the scientific and practical principles upon which the practice of pharmacy is based to the extemporaneous compounding of drugs and medicines and their distribution under proper conditions.

As the definition indicates, this course is the translation of the sciences underlying pharmacy into the art of pharmacy. It includes a detailed study of the prescription—the written order of the physician, dentist, or veterinarian—and of pricing, means of overcoming incompatibilities encountered in compounding improperly written prescriptions, dispensing of the finished medicament in a palatable form and possessing a suitable appearance, etc. It should be offered in the fourth year and a sufficient amount of time apportioned to it to train the student adequately.

Biological Sciences.—Pharmacognosy takes up the drugs and other materials obtained from the vegetable and animal kingdoms and emphasizes their identification and the establishment of their quality and purity by macroscopic, microscopic, and other

means. Experience is desirable with the use of scientific names and the standards of strength of potent drugs, the evaluation of purity and the means of detecting impurities in drugs subject to contamination and adulteration, sources, marketing, and identification. The course should be offered in the second year, with botany as a prerequisite.[1]

Pharmacology is the study of the effects produced by drugs on living organisms and the mechanisms whereby these effects are accomplished. It includes the relationship of these influences to **posology, therapeutics,** and **toxicology.** These are allied subjects taken up as integral parts of pharmacology, pharmacognosy, and other courses, the contents to be best mastered by such repetition. Pharmacology should also contain certain phases of **materia medica,** which is that branch of medical science which is concerned with the origin, composition, and properties of agents used in the treatment of disease. Therapeutics is the study of the uses of medicines and other agents in the treatment of disease. Posology is the science of dosage or a system of doses. Toxicology is the science of poisons, their actions, their detection, and the treatment of effects they produce.

The public demands that the pharmacist shall know at least the common or major therapeutic uses of the drugs which he sells and dispenses, the reasons for such uses, and the manner in which they are effective. It thus requires, in addition to some familiarity with the physical and chemical properties of the active constituents, information relative to the action of drugs.

The pharmacist should be acquainted with, and be capable of employing emergency steps in the treatment of, cases of poisoning and other bodily injuries (first aid). To accomplish this function, he must possess some knowledge of pharmacology. The pharmacist handles many medicaments that are very toxic, and some of these may easily be confused with less potent ones. An insight into the pharmacology of these potent substances should, at least, serve to impress the pharmacist with the necessity for continual care and caution in handling and dispensing them. His pharmacological information should be sound rather than minute or extensive.[2]

[1] *Ibid.*, pp. 142–156.
[2] *Ibid.*, pp. 156–175.

Since the pharmacist dispenses poisons, he is legally responsible for the distribution of potent drugs. He should therefore be versed in the doses of drugs in the Pharmacopoeia and the National Formulary, particularly in the case of those toxic to man and animal.[1]

The pharmacist is legally responsible for errors in prescriptions that result in poisoning. He is sometimes asked to give emergency treatment in cases of poisoning. Because of these responsibilities he should be well posted with the following points: (1) standard, lethal, and toxic doses of poisons, and factors for controlling them; (2) the poisonous action of drugs; (3) the symptoms of poisonous action of drugs; and (4) antidotal treatments and dangers involved in such treatments.[2]

Bioassay deals with the qualitative and quantitative analyses of drugs by means of the reactions of living organisms or tissues. Since it is vital for a pharmacist to know the standards for estimating the strength of the drugs and the preparations from them that he dispenses, and since such standards, in some cases, can be determined only by the action on animals, this course is required. The general principles involved in the technique of these assays are elucidated in the laboratory or by demonstration.[3] Pharmacology and bioassay should be studied in the third or fourth year of college.

Public health is a study of the principles of prevention and control of diseases by the use of drugs and the application of the pharmacist's knowledge and facilities to the promotion of the health and welfare of the public in cooperation with public and private health agencies. It includes a survey of municipal, county, state, and Federal health regulations.

Because of his accessibility to the public at large, the pharmacist is an influential agency for the dissemination of information concerning public health, and his cooperation with public health authorities in the control of communicable diseases is very important. He can accomplish this useful service only by being aware, at least in a general way, of the measures and programs conducted in this field.[4]

[1] *Ibid.*, pp. 175–177.
[2] *Ibid.*, pp. 210–217.
[3] *Ibid.*, pp. 122–123.
[4] *Ibid.*, pp. 187–210.

Hygiene and first aid are generally included in the public-health program, for they are closely allied in function. The pharmacist should be proficient in both fields. He is frequently called upon to render **first aid** in case of injury or sudden illness. By doing so, he may be able to save a life or prevent a dangerous infection before a physician becomes available. Also, many diseases and disorders may be controlled or even prevented by observing the rules of **personal hygiene.** Since the pharmacist is particularly fitted and in a strategic position to answer many of the questions of the layman relating to personal hygiene, he should be conversant with the latest recognized procedures for promoting this type of care. These subjects are best offered in the fourth year.

Pharmaceutical Chemistry.—At the beginning of this chapter an **applied course** was defined. On the basis of this definition, any course in chemistry offered in the pharmaceutical curriculum may be presented by qualified teachers in the schools and colleges of pharmacy; in such a course the principles and practical aspects of the particular field as well as the applications of these principles and aspects to pharmacy are stressed. In some cases, this form of presentation is highly desirable, for in a few basic courses offered in the departments of chemistry there is not sufficient time or inclination on the part of the instructor to stress those principles having particular application to pharmacy. This is particularly true in **qualitative pharmaceutical chemistry,** where the student should be proficient not only in the **schemes of identification of inorganic medicinal substances** in the Pharmacopoeia and the National Formulary but also in the tests for impurities in these, as well as being familiar with the incompatibilities that are apt to occur when chemical substances are brought into combination in prescriptions. This course is generally considered a second-year subject.

Quantitative pharmaceutical chemistry is quantitative chemistry in which special attention is paid to the assay methods of substances and their preparations in our official books. The course should be given in the second year, preferably, or in the third.

Organic pharmaceutical chemistry is general organic chemistry particularly devoted to the ever-increasing number of synthetic

organic medicinals becoming official. The course should be offered in the second year, preferably, or in the third.

Cultural and Elective Subjects.—Basic courses such as those discussed in Chap. III are those which are necessary to, or desirable for, the study of professional or applied subjects in the curriculum. In a pharmaceutical curriculum they might be considered of **cultural value** only when not **basic** or **professional** in character. **Cultural subjects** should broaden the viewpoint of the student and make him more intelligent and tolerant in his social, political, economic, and religious relationships, which are independent of his professional life.

The present-day pharmaceutical curriculum of 4 years, designed to prepare the student properly for the profession, permits the inclusion of only a few electives that have cultural value. For this reason it allows only limited freedom in the selection of these courses by the student. However, when provision is made for cultural subjects, the student should be permitted to choose those from which he feels he will derive the greatest benefit and enjoyment.

The following list, while it does not include all the subjects offered in a university or college that might have cultural value, is suggested to the student in pharmacy for consideration in electing this type of course to round out his undergraduate training:

English (first-year-college grade required)	Geology
English literature	History
Modern language	Political science
Philosophy	Psychology
General economics	Sociology
Geography	Speech or debating

Cultural courses, such as those listed above, are not basic or professional in character in so far as the pharmaceutical curriculum is concerned. However, if a student shows a particular aptitude in certain phases of his training or wishes to specialize in a particular branch of pharmacy, he may choose elective subjects that are professional and applied. If elected in the curriculum of 4 years, these choices may be made at the expense of the broad training to be derived by the selection of the cultural subjects listed above. The merits of semispecialization by means

of particularized professional and applied courses versus those of a broadened cultural training by means of well-selected cultural subjects should be examined carefully by the student.

The following are submitted as supplementary elective subjects of a professional and applied character:

Accounting (advanced)
Botany
  Plant physiology
  Taxonomy
Chemistry
  Biochemistry
  Microchemistry (chemical microscopy)
  Organic synthesis
  Physical chemistry
  Qualitative organic analysis
  Syntheses of drugs
Commercial art
Food analysis
Insecticides, parasiticides, rodenticides, and fungicides
Journalism
Mathematics (higher courses)
Hospital pharmacy
Manufacturing pharmacy
  Large-scale and semilarge-scale production
Perfumes and cosmetics
Photography
Physics (advanced courses)
Statistics
Veterinary pharmacology
Dental preparations

STUDY QUESTIONS

1. Define or explain the following: cultural subject; elective subject; professional course; applied course.

2. What is meant by the term prerequisite courses? Why are they necessary?

3. If a professional course is not required in a curriculum but is taken as an elective course, could it also be considered a cultural subject? State the reasons for your answer.

4. In what course might the principles of pharmaceutical ethics be developed? Explain your answer.

5. Discuss the importance of a course dealing with the literature of pharmacy. What faculty should be developed in studying this course?

6. Is the course in pharmacology required in the pharmaceutical curriculum to encourage counter prescribing by the pharmacist?

7. Why is it necessary for a pharmacist to have a knowledge of toxicology?

8. Discuss the importance to the pharmacist of a course in first aid.

9. What is public health, and why is a study of it imperative for the pharmacist?

10. What course in pharmaceutical chemistry is becoming of increasing value? Why?

COLLATERAL READINGS

"Basic Material for a Pharmaceutical Curriculum," McGraw-Hill Book Company, Inc., New York, 1927. See under various headings.

"Pharmaceutical Syllabus, The," The National Pharmaceutical Syllabus Committee, Chapel Hill, N.C., 4th ed., 1932; tentative 5th ed., 1942.

ALYEA, HUBERT N. *J. Chem. Education* **18**, 309–10 (1941).

ANON. "How a Training in Pharmacology Helps the Retail Druggist in the Successful Practice of His Profession," *J. Am. Pharm. Assoc. Practical Pharm. Ed.* **1**, 104 (1941).

ANON. "Why Pharmacognosy Is a Necessity in the Training of the Pharmacy Student and for the Work of the Practicing Pharmacist," *J. Am. Pharm. Assoc. Practical Pharm. Ed.* **1**, 158 (1941).

Committee on Curriculum and Teaching Methods, Report of the, *Am. J. Pharm. Education* **4**, 475–9 (1940).

GUTHRIE, C. L. "Practical Pharmacy and Dispensing," *J. Am. Pharm. Assoc. Practical Pharmacy Ed.* **1**, 69–71 (1941).

HOLCK, HARALD G. O. "The Value of Bioassay to the Pharmacist," *J. Am. Pharm. Assoc. Practical Pharm. Ed.* **1**, 258–9 (1941).

SWAIN, ROBERT L. "Jurisprudence in the Pharmaceutical Curriculum," *J. Am. Pharm. Assoc. Practical Pharm. Ed.* **1**, 273–4 (1941).

Other papers dealing with pharmaceutical education may be found in the *Journal of the American Pharmaceutical Association* and its *Practical Pharmacy Edition* and the *American Journal of Pharmaceutical Education*, especially reports of the Problems and Plans Committee of the American Association of Colleges of Pharmacy on dispensing pharmacy and pharmacological and biological subjects.

CHAPTER V

BRANCHES OF AND OPPORTUNITIES IN PHARMACY

The wise and active conquer difficulties by daring to attempt them.—Nicholas Rowe.

Pharmacy is an ancient and honorable profession. Its beginnings are lost in the mists of antiquity and its history is replete with substantial accomplishments. Pharmacy is the mother of medicine and the original source of many forms of research. Numerous investigators, who have made epochal contributions to science and art, have been enrolled among its followers. Today pharmaceutical research is scholarly and productive. In the laboratories . . . scientists are industriously and effectively studying the problems of the field.

At the present time, however, the profession is undergoing a heavy barrage of criticism. The assertion has been made that it has been commercialized and has sunk to a level of soda fountain dispensing and rule-of-thumb shopkeeping. . . . It is asserted that the profession usurps the functions of the doctor by counter prescribing and that it is pseudoscientific without an intelligent grasp of the sciences it pretends to utilize. Some critics say that in the effort to commercialize the occupation, the ancient professional morale has been lost with the result that the occupation has ceased to be a profession and has now become a trade.

It is, therefore, of interest to examine this vocation which in numbers is not inconsiderable and in history is rich and worthy. It is a matter of major social importance to know with some definiteness just what the pharmacist does, what place he fills or may fill in society, how much he needs to know, and what sort of training should be given him in order that he may properly and intelligently fulfill his functions. The criticisms just enumerated become immaterial if a picture can be drawn showing the full round of the responsibilities of the pharmacist and the amount, depth, and extent of the training which is needed to fit him adequately to fulfill his obligations.[1]

[1] "Basic Material for a Pharmaceutical Curriculum," McGraw-Hill Book Company, Inc., New York, 1927, p. 1.

It was for the purpose of determining the extent of the obligations and duties of the pharmacist, and the kind and amount of training required to prepare him for these responsibilities, that the entire investigation described in "Basic Material for a Pharmaceutical Curriculum" (sometimes called the "Charter's Report" or "The Report of the Commonwealth Committee") was carried out. After a 2-year survey the director of the study was convinced that pharmacy is a profession rather than a trade.[1] In the preceding chapters of this text this conception has been stressed repeatedly. We are now in a position to discuss, without doubt of its status, the opportunities of pharmacy.

The Branches of Pharmacy.—The branches or fields of pharmacy, as a public health profession, may be classified as **retail pharmacy, professional pharmacy,** and **hospital pharmacy,** it being kept in mind that under certain conditions there is no clear distinction among the fields, especially between the first two, which, of necessity, must be profitably operated as businesses in order to maintain their existence. These three branches offer ample opportunity for a successful ethical and economic practice of the profession. The distinctions among the three classes of pharmacy cannot be sharply defined since every registered pharmacist should be professional and ethical in all his business activities.

Retail or commercial pharmacies may be divided into two types: (1) the semiprofessional pharmacy, which is becoming more common in the United States and in which the attention and the efforts of the pharmacist are divided between the professional practice of pharmacy and the merchandising of side lines usually related to, and having their origin in, the pharmacy. The professional practice of pharmacy tends to predominate over the commercial interests of the business. (2) The "drugstore" is exemplified by the type of establishment usually managed by a chain-store corporation or by an independent proprietor who is striving under difficulties to employ chain-store methods or by the one-man type of store. In this group there is usually an intensification of the commercial lines with a distracting submergence of the professional departments, result-

[1] *Ibid.*, p. 13.

ing in an almost complete lack of interest in the practice of pharmacy.

Retail pharmacies of the first type occur generally in residential or business sections of our large cities and in all communities of 2,000 inhabitants or more. Those of the second type usually are found in highly congested business districts and in residential sections of our larger cities and in smaller communities in which too many stores exist on the basis of population or which are too small to support an establishment of the first type.

Professional pharmacies are those which are conducted in a profitable manner and yet are strictly pharmaceutical in operation. These may be located in or near medical centers or communities in an area where there is a sufficiently large population and where other conditions warrant the offering of the finest type of professional service. The ideal pharmacy of this type possesses the proper physical equipment and medical supplies, sufficient space for manufacture and dispensing, and an adequate library for study and research. The pharmacist working in such an environment should be able to give the fullest cooperation to the physician, the dentist, the veterinarian, and public health authorities. In return, he should be well remunerated for rendering specialized scientific and pharmaceutical services. He may be asked to perform clinical and bacteriological tests, prepare certain biological products, supply sterile solutions, etc. The only side lines such a pharmacy would display and sell would be surgical supplies and other items of a related character (see Chap. II, pages 54 to 56).

It must be kept in mind, however, that a pharmacy located in a residential or a business section or in a small community may be just as professional as the one described above and yet may need other sources of income in order to produce a volume of sales which will qualify the business as **profitable**—and the operation of a pharmacy is as much a business as the operation of any type of nonprofessional store. Furthermore, it is entirely possible for the prescription departments of a large chain "combine" or a department store to function on a highly professional basis, although in this group the overemphasizing of pursuits other than pharmaceutic is in great evidence.

• **Hospital pharmacies,** as the name signifies, are professional pharmacies that are located in hospitals of various types and that may or may not be conducted for profit. They are rapidly

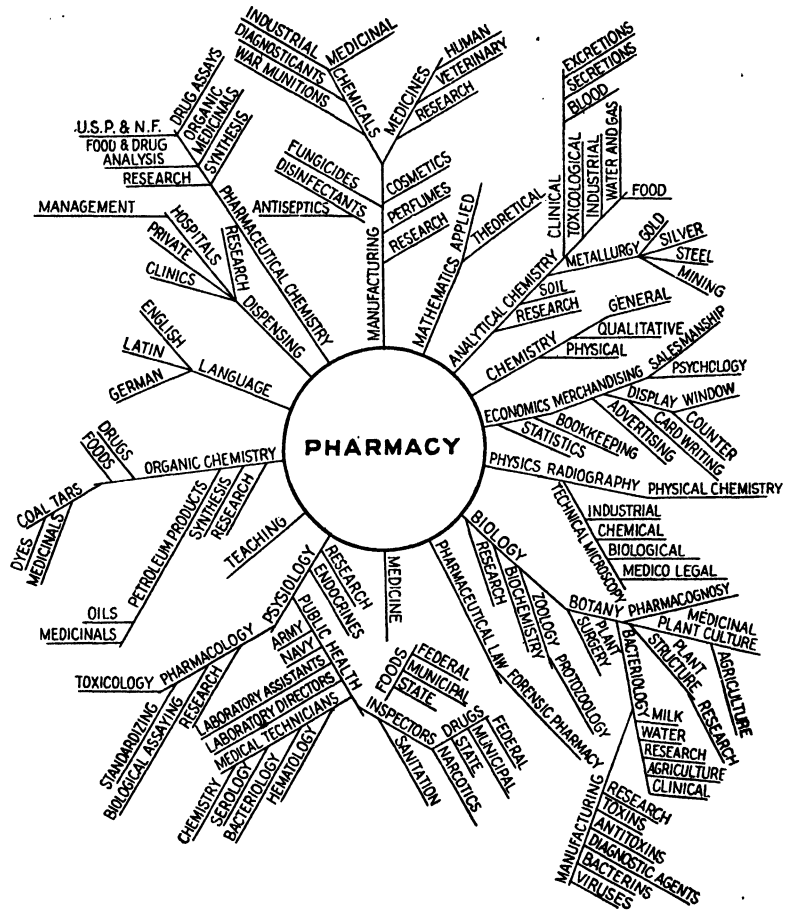

FIG. 1.—Professional occupations which might be followed with a sound training in pharmacy.

increasing in number owing to a belated realization on the part of hospitals of the value and necessity of an adequate pharmaceutical service. In the maintenance of such a pharmacy the pharmacist is in a position to perform outstanding professional

work and preserve the highest professional standards. Such pharmacies operating under special privileges—such as tax-free alcohol—should refrain from conducting retail pharmacies in competition with existing establishments in the city or community that are trying conscientiously to give adequate pharmaceutical service.

In conclusion, it must be kept in mind that a retail store of a semiprofessional type may be more ethical in its practices than a professional or hospital pharmacy that merely pretends to be professional in all its engagements.

The Opportunities of the Profession.—A well-balanced and well-selected pharmaceutical educational program of 4 years, as outlined by the Pharmaceutical Syllabus and recognized by the American Council on Pharmaceutical Education, is a blending of the theoretical and applied educational processes; it offers a sound training for the practice of the profession and also opens several avenues for gainful employment, instead of one, as straight academic courses so often do. It has few equals for all-round practical usefulness. Although schools of pharmacy should not be essentially a training ground for other professions and fields but should serve principally to put graduates of the highest type into retail and hospital pharmacy, this broadness of program does offer opportunity for other students whose inclinations are in other directions. The graph on page 87, in a revised form (Fig. 1), illustrates not only the ramifications of the profession but also the numerous possibilities of allied specialties that may easily be developed.[1]

Retail pharmacy attracts a majority of the graduates of our colleges of pharmacy, who enter *retail stores* as registered pharmacists with salaries ranging from $120 to $300 per month. They may become managers at higher salaries, or proprietors. Proprietorship is the aim and desire of most of the pharmacists entering this branch, especially in the smaller communities. Such ownership may be profitable when the location of the business is chosen with due consideration for the population to be served, the competition involved, and the nature of the surroundings—whether industrial, residential, a business zone,

[1] H. B. Carey. *J. Am. Pharm. Assoc.* **26**, 335–40 (1937).

etc.—and when proper professional service is offered and sound business principles are applied. With higher educational requirements, the demand for energetic, honest, and sincere registered pharmacists has increased, and even in times of depression opportunities for steady employment are present. Working conditions from the standpoint of hours and compensation need adjustment.

Professional pharmacy as a career presents a real opportunity to the graduate in pharmacy who is primarily interested in the professional and manufacturing aspects of pharmacy as well as interprofessional relationships. After a period of more than fifty years of retrogression in this country there is a slowly and steadily developing renascence of professional pharmacy, and the future seems heartening. Most professional pharmacies offer proper working conditions and remuneration and command the respect of the allied professions. Proprietorship, especially of a new establishment, should be considered carefully. A reserve of capital funds to sustain the business for at least a year might be necessary before it shows profit.

Hospital pharmacy offers a valuable type of experience in the form of internships. It presents exceptional opportunities to those pharmacists, especially women, who are interested in providing adequate pharmaceutical service of a strictly professional character to the hospitals of our country. Advancement to chief pharmacist or even to manager or superintendent of the hospital or some other rank is the reward for conscientious effort and professional zeal. Working conditions are satisfactory, but salaries in general need adjustment.

Departments of **municipal, county, state, and Federal services** offer many varied opportunities to the graduate. Large municipalities have occasion to employ pharmacists in dispensing drugs in city hospitals and other divisions of civic management and in laboratories of various types established for the maintenance and enforcement of law and order and the improvement of civic welfare. In some cities appointments are made under civil service regulations.

Counties and states, often on a larger scale than municipalities, require the service of pharmacists in the dispensaries of their hospitals and in the enforcement of laws regulating the diverse

professions that are concerned with the welfare of the general public.[1]

Of significance is the gradual recognition of pharmacy in the several divisions of the Federal government. These include the Army, the Navy, the Public Health Service, the Alcoholic Administration, the Bureau of Narcotics, the Food and Drug Administration, and the Veterans Administration.

The Personal Classification Division of the United States Civil Service Commission places pharmacy in the **professional service, subprofessional service,** and **scientific service.** Two grades are offered for the registered pharmacist: pharmacist, at $2,000 to $2,600 a year, and pharmacist's assistant at $1,620 to $1,980 a year. No grades are established for the registered assistant.[2] In 1939, examinations were offered for the position of junior pharmacist, requiring graduation from a 4-year course. Those passing the examination successfully were eligible to the following positions: druggist, United States Marine Hospital, $1,800 a year; assistant pharmacist aide, Veterans Administration, $1,620 a year; junior food and drug inspector, Food and Drug Administration, $2,000 a year; junior toxicologist, Chemical Warfare Service, $2,000 a year; junior narcotic agent, Bureau of Narcotics, $2,000 a year.[3,4]

In 1944 the position of Chief Pharmacist was created in the Veterans Administration which, for the first time, enables pharmacists to obtain a P-2 rating at $2,600 to $3,200 per year. In institutions where there is one Pharmacist and two or more Pharmacist's Assistants, the practitioner with the rating of Pharmacist will be promoted to the P-2 grade. This rating will be attained primarily through promotion of key personnel in the lower grade. Other pharmacists employed in the facilities of the Veterans Administration are rated as Pharmacist, P-1, at $2,000 to $2,600 per year or as Pharmacist's Assistant, SP-4, at

[1] ELMER A. GESSEL. *Am. Professional Pharmacist* **5**, 503, 506, 529, 532 (1939).

[2] PAUL J. THOMAS. *J. Am. Pharm. Assoc.* **21**, 692–3 (1932).

[3] "Report of the Committee on Pharmacists in the Government Service," *Am. J. Pharm. Education* **4**, 434–9 (1940).

[4] A. S. ERNEST. *J. Am. Pharm. Assoc. Practical Pharm. Ed.* **1**, 301–4 (1940).

$1,620 to $1,920. At present 120 or more pharmacists, male and female, are employed in the Veterans Administration. This number will be increased as expansion and necessity demand.

In the United States Navy, every ship has a medical department, of which one of the units is a dispensary. In 1937, there were 75 large and 125 small dispensaries. As this branch of defense is enlarged to a two-ocean navy, the number of medical departments and therefore of dispensaries is being greatly increased. In the present organization of the Hospital Corps the following ratings are established: (1) Chief Pharmacist (Commissioned Warrant Officer), (2) Pharmacist (Warrant Officer), (3) Chief Pharmacist's Mate (Chief Petty Officer), (4) Pharmacist's Mate—First Class (First Class Petty Officer), (5) Pharmacist's Mate—Second Class (Second Class Petty Officer), (6) Pharmacist's Mate—Third Class (Third Class Petty Officer), (7) Hospital Apprentice—First Class, (8) Hospital Apprentice—Second Class. It can readily be seen that opportunity for advancement is available to men in this service who have a pharmaceutical training.[1]

In 1936, 16 commissions as second lieutenant were established in the **Medical Administrative Corps** of the United States Army, and more were necessary as the Army was expanded. In 1940, pharmacists chosen under the Selective Service Act were given full army recognition for their professional training and experience; those with a 4-year course who qualify are now being granted a second lieutenant's commission until the pharmaceutical needs are filled and are placed in the **medical department** of the Army and the **Medical Administrative Officers' Reserve Corps.** Pharmacists who do not meet the educational and other requirements for a commission are qualified for the special noncommissioned status of pharmacist with the rank of technical sergeant—$1,008 and sustenance annually—must take 3 months' training at camp, and, when a vacancy occurs, are transferred to the Medical Corps and given the noncommissioned status. The officers commissioned in this corps will, by recent legislation, be retained in the newly established Pharmacy Corps.

The Pharmacy Technician School of the **United States Army** was established in 1939. Twenty enlisted men were selected

[1] E. G. SWANN. *J. Am. Pharm. Assoc.* **26**, 657–60 (1937).

and after 1,140 hr. of training were assigned as technicians and assistants to those performing the pharmaceutical work of the Army.[1,2]

In July, 1943, the **Pharmacy Corps** was established, by legislation, in the United States Army, its personnel to "consist of seventy-two officers in the grades of colonel to second lieutenant, inclusive. Appointments . . . shall be made in the grade of second lieutenant from pharmacists between the ages of twenty-one and thirty-two who are **graduates of recognized schools or colleges of pharmacy requiring four years of instruction for graduation.** . . . "[3]

In the **Public Health Service,** in the **Alcohol Administration,** and in the **Bureau of Narcotics,** there is a demand for pharmacists as inspectors, technicians, and other types of laboratory worker.

With the enactment of the Federal Food, Drug, and Cosmetic Act of 1938, the regulatory duties of the **Food and Drug Administration** have been greatly increased. This affords more openings as inspectors, assayists, etc., of interest to the pharmacist.

The Marine hospitals, 26 in number, with more than 6,000 beds, provide opportunity for pharmacists. This service began in 1799 as the Marine Hospital Service and continued as such until 1902, when it became the United States Public Health and Marine Service. It changed, in 1912, to the United States Health Service.[4]

The extensive problems of the **Veterans Administration** in hospital and rehabilitation work, etc., also present opportunities to the graduate of pharmacy.

Opportunities in Other Fields.—Medical and surgical supplies must be prepared and manufactured. To meet this demand there are **manufacturing pharmacists, manufacturing plants,** and **industrial laboratories,** varying from small concerns producing a limited line to manufacturing houses with extensive research

[1] "Report of the Committee on Pharmacists in the Government Service," *Am. J. Pharm. Education* **4**, 434–439 (1940).

[2] GLENN K. SMITH. *J. Am. Pharm. Assoc. Practical Pharm. Ed.* **1**, 296–8 (1940).

[3] Boldface type by authors.

[4] CLAUDE V. HOPE. *Am. Professional Pharmacist* **4** (No. 12), 27–9, 32 (1938).

and industrial activities and employing chemists and pharmacists for control, testing, and research work involving medicines, cosmetics, biologicals, insecticides, etc.

Where medicinal products are manufactured, they must be promoted and distributed. This is accomplished by legitimate wholesale concerns and the manufacturers, who detail trained men as their representatives to the pharmaceutical and medical professions. These should be registered pharmacists, physicians, dentists, or veterinarians.

The Pharmacist in Graduate Work and Research.—As medical science advances, so must pharmaceutical education, the training of pharmacists, and the practice of pharmacy. To qualify as a research worker in the laboratories of a pharmaceutical manufacturer or in his own manufacturing plant, a pharmacist in this branch of scientific work will find that graduate study for the master of science and the doctor of philosophy degrees in a recognized university is of advantage.

Such advanced training is also necessary if one is interested in **pharmaceutical education** and desires to undertake **teaching** in one of the branches of the pharmaceutical curriculum in a reputable school of pharmacy.

Women in Pharmacy.—It has been stated that 4 per cent of the registered pharmacists are women, and it is probable that this figure, at present, is low. Hospital pharmacy, professional pharmacy, and, increasingly, retail pharmacy are presenting opportunities to women pharmacists, although seldom as managers or proprietors. Openings exist in laboratories, government work, and teaching. A few states have passed laws prohibiting nightwork for women in pharmacy. The profession provides as adequate an opportunity for employment to women as others do, provided that an equitable salary scale and satisfactory working hours and conditions are maintained.

Other lines of vocation that might be selected by the graduate in pharmacy do not need further elaboration, since only those directly related to the pharmaceutical field require discussion. The specialized selections may be observed in the chart on page 87.

It is reasonable to say that a student in pharmacy who pursues the curriculum with serious purpose and steady effort, who

determines early in his career what branch or service he desires to follow, and who plans his program of education accordingly is assured of a vocation with ample opportunities and security.

STUDY QUESTIONS

1. What study has been made to determine whether pharmacy is a profession or a trade?
2. What is meant by a public health profession?
3. What are the branches of pharmaceutical practice?
4. Distinguish between the semiprofessional pharmacy and the present-day "drugstore."
5. Discuss the activities of the professional pharmacy.
6. What are the opportunities of the pharmacist in governmental divisions?
7. In what branches of the armed services is there opportunity for the pharmacist?
8. What advanced degrees are offered in schools of pharmacy?
9. Why is the pharmaceutical curriculum worthy of consideration by one who desires a well-rounded training?

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The above list is not intended to be a complete bibliography of the many articles that have been written of the opportunities in pharmacy but gives typical examples that help to build up a more complete idea of the branches and opportunities of pharmacy. For other titles, the reader is referred to the *Journal of the American Pharmaceutical Association*, the *American Professional Pharmacist*, *American Journal of Pharmaceutical Education*, etc.

CHAPTER VI

THE ESSENTIAL PHARMACEUTICAL LITERATURE

One of the ways of judging a profession is by its literature. Pharmacy has a literature that is not sufficiently well known or appreciated by American pharmacists. Historical pharmaceutical literature is not abundant but is sufficient to give readers much information concerning pharmacy as practiced by the ancients as far back as our written records extend. The history of pharmacy is closely tied up with that of medicine, and a knowledge of the art and science of pharmacy can be acquired also from the books on the history of medicine.

Historical evidence indicates that only in comparatively modern times has pharmacy been entirely in the hands of pharmaceutical specialists or pharmacists. The head of the household, family, or clan was often the doctor, pharmacist, and nurse to those under his care, even including the domestic animals. Such a person was not professionally trained in either pharmacy or medicine but had a practical working knowledge of them. Much of the lore of herbs and remedies has come to us from such persons, and there is no reason for discarding the information that has come down to us from these sources. Rather, we should accept it as a part of the history and literature of the profession, and be tolerant of it in the light of science and professionalism.

If American pharmacy is to continue and to thrive as a profession, pharmacists must become truly professional in training and practice. A study of the literature of pharmacy should aid in accomplishing such a desirable end.

It is the responsibility of the schools of pharmacy to acquaint their students with the literature of pharmacy. This means that a library of considerable size, containing adequate, practical, and usable reference material, should be easily accessible. In addition, the schools should offer courses dealing with the literature, in which reading assignments upon various subjects

are made, to acquaint the student with this material and to help him form the habit of seeking out the proper sources for all kinds of information.

The pharmacist's library has been discussed in Chap. II. Though it is difficult to prescribe the contents, the modern professional pharmacist should have a library worthy of the name. It would naturally have to be limited as to the number of books and journals but should contain a sufficient number of each to be of reference value and to cover the problems of medical and pharmaceutical interest.

Pharmacopoeias.—It has been stated that a pharmacopoeia is a chapter in the history of civilization. If one took the time to study all that precedes, enters into, and follows the issuance of a pharmacopoeia, he would appreciate the significance of this statement. It is possible, certainly, to judge the medical, pharmaceutical, and scientific progress of a country by studying the successive revisions of its pharmacopoeia. This reflects in a general way the progress of a country as a whole, as is well illustrated by our Pharmacopoeia of the United States of America. In the late sixties and the seventies there was frequent criticism of the Pharmacopoeia, indicating that it was not up-to-date or adequate for the time. As a result, the sixth edition of the Pharmacopoeia (1880) was thoroughly revised. The student needs only to compare one revision with its predecessors to understand the remarkable changes that were made. This reflects the demands of a rapidly growing America. It was in keeping with the organization of state pharmaceutical associations, the creation of state boards of pharmacy, and the founding of schools of pharmacy at state universities throughout the country.

More recently it has been decided to revise both the Pharmacopoeia and National Formulary each 5 years, rather than each 10 years. Even prior to 1940, interim revisions of the Pharmacopoeia appeared. At the present time, supplements to both these standards are being issued in an effort to meet the demands for changes in formulas and to supply new ones. Emergencies such as war naturally make for an increased number of changes.

By 1939 there were more than 20 pharmacopoeias, from as many countries, mostly in the Western World, which were in use and revised from time to time. None has been revised

with the same regularity as the Pharmacopoeia of the United States of America, which has been revised every 10 years from 1820 to 1940.

The pharmacopoeias of the world are listed and described in the two following books: "Plantes officinales" by Bruntz and Jaloux (1918), in French; and "Die Arzneibücher" by Falck (1920), in German. Nothing has appeared in English upon the subject of pharmacopoeias that compares with these two reference books, which should be in the library of every school of pharmacy.

In almost every case, state and national pharmacopoeias were preceded by city pharmacopoeias. In Europe there were many of the latter in France, Belgium, Holland, Italy, England, and Germany. The first of these to appear was the "Pharmacopoeia Augustana," published in Augsburg in 1564. It has been reproduced by the State Historical Society of Wisconsin in collaboration with the Hollister Pharmaceutical Library Fund. This is an interesting text in facsimile accompanied by an appropriate historical explanation by Theodor Husemann.

Another very popular city pharmacopoeia of the eighteenth century was the "Pharmacopoeia Wirtenbergica," of 1741. It listed 1,952 different drug items and formulas, which was 852 more than appeared in the "Pharmacopoeia Augustana." Other German city pharmacopoeias were those of Hanover (1706), Saxony (1779), and Münster (1739). These all went through several editions. In 1872, following the creation of the new German Empire in 1871, the first "Pharmacopoeia Germanica" was issued by governmental edict. This made it the pharmaceutical standard for the whole of Germany.

In France there were many private pharmacopoeias, written by famous pharmacists (see pages 22–25). City pharmacopoeias in France were those of Paris, "Codex medicamentarius seu pharmacopoeia Parisiensis" (1630); of Lille, "Pharmacopoeia Lillensis" (1640); of Bordeaux, "Pharmacopoeia Burdigalensis" (1643); and of Lyon, "Pharmacopoeia Lugdensis" (1778). The first national pharmacopoeia for France followed the stabilization of the French Republic and was issued in 1818; it was entitled "Codex medicamentarius seu pharmacopoeia Gallica."

The first official pharmacopoeia of Europe was that of the "Ricettario Fiorentino," issued in 1498 and made obligatory

in Florence. In 1559, the "Antidotarium Mantuanum" for Mantua appeared, followed in 1574 by the "Antidotarium Bononiense" in Bologna. The term *pharmacopoeia* was first used in Italy in connection with the "Pharmacopoeia Bergamensis" (1850) in Bergamo. In Venice, the "Pharmacopoeia Veneta" appeared in 1618, the "Pharmacopoeia Taurinensis" in Turin, and the "Pharmacopoeia Parmiensis" in Parma in 1823. A national pharmacopoeia for Italy was first issued in 1892, entitled "Farmacopoeia ufficiale del regno d'Italia."

In England there were three city pharmacopoeias that were official throughout the kingdom prior to 1864. They were those of London, Edinburgh, and Dublin. The "London Pharmacopoeia" first appeared in 1618, the "Edinburgh Pharmacopoeia" in 1699, and the "Dublin Pharmacopoeia" in 1807. These were all replaced by the "British Pharmacopoeia" in 1864. This first issue was superseded by a second revised edition in 1867.

In this brief statement concerning European pharmacopoeias no attempt has been made to mention all the city pharmacopoeias or even to name all the countries having such standards. It should serve to introduce the subject of national pharmacopoeias, which were rather slowly made obligatory in otherwise well-established states. From a historical point of view each new national pharmacopoeia was evidence of an increasing unity among each of the states, politically and pharmaceutically.

The dates of the first appearance of 20 of the leading national pharmacopoeias are given below in chronological order.

1772 "Pharmacopoeia Danica"
1775 "Pharmacopoeia Svecica"
1794 "Pharmacopoeia Hispana"
1812 "Pharmacopoeia Austriaca"
1818 "Pharmacopoeia Gallica"
1819 "Pharmacopoeia Fennica"
1820 "Pharmacopoeia of the United States of America"
1851 "Pharmacopoeia Neerlandica"
1854 "Pharmacopoeia Belgica"
1854 "Pharmacopoeia Norvegica"
1862 "Pharmacopoeia Romana"
1864 "Pharmacopoeia of Great Britain"
1865 "Pharmacopoeia Helvetica"

1866 "Pharmacopoeia Rossica"
1871 "Pharmacopoeia Hungarica"
1872 "Pharmacopoeia Germanica"
1874 "Farmacopoeia Mexicana"
1876 "Pharmacopoeia Portugueza"
1886 "Pharmacopoeia Japonica"
1892 "Farmacopoeia ufficiale del regno d'Italia"

Pharmacopoeia of the United States.—The physicians and apothecaries who came to America with the early settlers naturally used the pharmacopoeias and other such works of reference as were available. Among these were the pharmacopoeias of London, Edinburgh, and Dublin. Books in other languages were not used extensively in medicine and pharmacy in early America.

The first American pharmacopoeia was the so-called "Lititz Pharmacopoeia," which appeared in 1778. It was a 32-page booklet for use by the Military Hospital of the United States Army, published at Lititz, Pa. It had the imposing title, "Pharmacopoeia Simpliciorum et Efficaciorum" and was divided into two parts. Part I was a list of 84 internal remedies, and Part II included 16 preparations for external use. It must have served a useful purpose as evidenced by the fact that it was revised in 1781.

During the last decade of the eighteenth century there was talk of an American pharmacopoeia by the physicians of Philadelphia. The Medical Society of South Carolina projected an independent American materia medica. Neither of these ideas materialized. However, the "Pharmacopoeia of the Massachusetts Medical Society" made its appearance in 1808, listing 536 drugs and preparations, among which were drugs indigenous to America. The separation of the professions of pharmacy and medicine was, by this time, well established as is clearly indicated in the preface of the book. The book was adopted by the apothecaries of Massachusetts; but though it was hoped that it would meet with general acceptance, it did not do so.

The "Pharmacopoeia of the New York Hospital" was issued in 1816 by the authority of the physicians of the New York Hospital. It was termed a manual of prescription practice and a selection of officinal preparations. It was doubtless a useful formulary but was not a state pharmacopoeia.

A project for a national pharmacopoeia was submitted by Dr. Lyman Spalding to the New York County Medical Society on Jan. 6, 1817. It was Spalding's plan to hold a general convention of delegates from all the medical societies and schools in order that they might have a part in compiling the new book. It was proposed that the states should be divided into four districts, each to hold a convention and formulate a pharmacopoeia. The general convention would then prepare a national pharmacopoeia from the four district pharmacopoeias. Only two of the districts held conventions as planned. The general convention was convened in Washington in January, 1820. On Dec. 15, 1820, "The Pharmacopoeia of the United States of America, 1820, by the authority of the Medical Societies and Colleges," made its appearance. It was printed both in Latin and in English because, in those days, every well-educated physician and apothecary knew Latin.

It is stated that more than 90 per cent of the material in the "Massachusetts Pharmacopoeia" was included in this first Pharmacopoeia. This makes the former book a precursor to the latter. The new book was well received, although not entirely without criticism, and was reprinted in 1828. This was not a revision, and the only changes in text were corrections in spelling. For interesting details concerning this first edition of the Pharmacopoeia the reader is referred to the historical introduction of the current revision.

At the first general convention at Washington in 1820 it was agreed that a second general convention should be held in January, 1830. Through some misunderstanding there were two conventions and two pharmacopoeias in 1830. One convention was held in New York City. In November, 1830, the so-called "New York Pharmacopoeia" was published, "by the authority of the General Convention for the Formation of the American Pharmacopoeia." While plans were proposed for calling a convention in 1835 for purposes of revising the "New York Pharmacopoeia," the convention was not called and there were no successors to the book.

The Washington convention accepted the revised draft of the 1820 Pharmacopoeia as submitted by the Philadelphia delegates as a basis for a new edition. The new book was printed in

Philadelphia in 1831 "by authority of the National Medical Convention, held at Washington, A. D. 1830." The Philadelphia revision soon gained wide acceptance and superseded its rival, the "New York Pharmacopoeia." The so-called "Philadelphia Pharmacopoeia" has been revised each 10 years since 1830 up to 1940. It will be revised again in 1945 and each 5 years thereafter.

The Pharmacopoeias of 1820, 1830–1831, and 1840 were the work of physicians, with some help from pharmacists without recognition for the latter. At the convention of 1850, held in Washington on May 6, 1850, five pharmacists were privileged to attend the convention, and two were made members of the Committee of Revision. This was further recognition of pharmacy. From that time on the number of pharmacists on the revision committee increased until about two-thirds of the committee of 50 are pharmacists or represent fields of pharmacy.

It should be observed that the Pharmacopoeia, from the beginning, was a standard set up by the medical profession and not issued in compliance with an edict from the government. It became a legal standard in 1906, following the passage of the Federal Food and Drugs Law of that year, and is today one of the three legal standards, used by the Federal government in the enforcement of the Federal Food, Drug, and Cosmetic Act of 1938. These standards are also acceptable to those entrusted with the enforcement of similar laws in the several states.

The problem of revising the Pharmacopoeia is the task of the Committee of Revision, which is elected by ballot from nominations made from the floor at a session of the United States Pharmacopoeial Convention set aside for the purpose. The number of nominees is not limited. The 50 receiving the highest number of votes are declared elected to the revision committee, which meets during the convention period to elect its chairman. The details of revision are carried on by subcommittees formed, usually by agreement, from the committee members. A person may be a member of more than one subcommittee. Each subcommittee elects its chairman.

There were 15 regular subcommittees for the twelfth revision of the Pharmacopoeia. There were also 9 additional committees and boards, which gave valuable service in an advisory capacity

upon many important products and problems referred to them. The Pharmacopoeia is the property of the Board of Trustees of the United States Pharmacopoeial Convention. Business and legal matters pertaining to it are disposed of by this board.

Pages I to LXXXVIII of the Pharmacopoeia XII, among other items, contain a list of the Executive Committee and Subcommittees, Preface, The History of the United States Pharmacopoeia, Articles of Incorporation, Abstract of Proceedings, Membership of the United States Pharmacopoeial Convention of 1940, General Principles Recommended by the United States Pharmacopoeial Convention of 1940 to be followed in revising the Pharmacopoeia, and International Protocol (P.I.) Standards. Pages 1 to 8 comprise the General Notices, followed by the Monographs on Vegetable and Animal Drugs, Chemicals, and Preparations, extending from pages 9 to 550. Pages 551 to 825 give extensive information on the subjects of General Tests, Processes, and Apparatus, followed by an index of 55 pages.

There is little realization of the tremendous amount of work that goes into the revision of the Pharmacopoeia. Most of the work is done gratis by members of the profession; otherwise, the price of the book would be prohibitive. Much more could be written concerning the Pharmacopoeia, but the student is referred to the book itself for interesting and informative details.

The National Formulary.—It is customary to attach greater importance to pharmacopoeias than to formularies. In Europe, when regulations concerning uniformity in medical practice became necessary, formularies appeared. They were known by many titles such as the "Riccettario," "Antidotarium," "Formulario," "Thesaurus," "Enchiridion," and "Dispensatorium." The term pharmacopoeia gradually replaced these various titles for the official standards. The term *codex* is used in connection with the titles of the French pharmacopoeia and the "British Pharmaceutical Codex." The latter book is a legal standard in parts of the British Empire but is not a pharmacopoeia; therefore, the use of the term *codex* is acceptable.

There are formularies of many kinds in the United States, both pharmaceutical and technological. It is not possible to discuss these in detail, but mention should be made of the fact

that hospital formularies are increasing in number. These add to the convenience of the hospitals in manufacturing and dispensing the drugs and medicines used in them. Since hospital formularies are prepared for local convenience, not many of them are of general interest or use. The formulary that deserves special mention is the National Formulary.

The National Formulary was first published in 1888. It has been revised each 10 years since then, the seventh and latest edition appearing in 1942. Like the Pharmacopoeia, it will be revised each 5 years in the future. The Committee of Revision of the National Formulary is comprised of 10 men elected by the Council of the American Pharmaceutical Association. The chairman of the committee is elected in the same manner, and each member of the committee is chairman of a subcommittee that is responsible for revising a certain division of the book. With the approval of the council, the subcommittee chairmen choose the members to serve with them on their subcommittees. The National Formulary, like the Pharmacopoeia, is a legal standard, being accepted as an authoritative reference in matters of legislation.

The "New York and Brooklyn Formulary," which was published in 1884, is looked upon as a precursor to the National Formulary. The idea of such a formulary as the latter was in the minds of the members of the American Pharmaceutical Association and was given much consideration, over a period of many years, before it was finally issued.

The present arrangement of the National Formulary is similar to that of the Pharmacopoeia, *i.e.*, the monographs are arranged alphabetically according to Latin titles. The first five editions, however, were different in arrangement. The **simples** comprised one part and the **compounds** another part of the monographs. This is mentioned because it illustrates the plan of arranging the material in old formularies and pharmacopoeias. The National Formulary is the property of the American Pharmaceutical Association, and the Council passes upon matters pertaining to it and directs the printing and distribution of the book.

There is close cooperation between the Committees of Revision of the Pharmacopoeia and the National Formulary. By this means no monograph that appears in one book is duplicated in

the other in concurrent revisions. It often happens that a monograph which has appeared in a prior issue of either book is adopted by the companion book. This is done by agreement or after the title has been deleted from one text or the other.

The sixth and seventh editions of the National Formulary are great improvements over earlier issues. These have increased the popularity and usefulness of the book, which should be found, along with the Pharmacopoeia, in every pharmacy. Among its valuable features are the monographs on "Reagents and Preparations for Use in the Clinical Laboratory," "Ingredients of Reagents and Preparations for Use in the Clinical Laboratory," and "General Tests, Processes, and Apparatus," on pages 487 to 614.

The "Homeopathic Pharmacopoeia of the United States" appeared first in 1897. The fifth and most recent edition was released in 1938. It is recognized as a standard in the enforcement of the Federal Food, Drug, and Cosmetic Act.

American Dispensatories.—Dispensatories are extensive commentaries on official and unofficial drugs and pharmaceutical products. They are accepted for their value as reference books by physician and pharmacist alike. They have been well developed and extensively used in America. The first dispensatory to appear in the United States was the "American Dispensatory," published in 1806 by John Redman Coxe. This book went through five editions, the last appearing in 1831. In 1810, Dr. James Thatcher edited "The American New Dispensatory" by order of the Massachusetts Medical Society. It went through four editions, the last appearing in 1821. In 1833, George B. Wood and Franklin Bache published "The United States Dispensatory." It was revised many times by the original editors and has been kept up-to-date by its friends for many years and through many editions and revisions, the latest being the twenty-third edition published in 1943.

"The National Dispensatory" first appeared in 1879, published by Alfred Stillé and John Maisch. It went through five editions, the last appearing in 1896. This book was continued in 1905 under the title "The National Standard Dispensatory," being completely rewritten and revised by new editors.

In 1852, John King and Robert S. Newton edited a different kind of dispensatory, entitled "Eclectic Dispensatory of the United States." Up to 1909 the book had 19 editions. The text was devoted to those drugs and formulas of interest to the American eclectic school of medicine. The eclectic school of medicine, which originated in America, was a movement in opposition to the established practice of using drastic remedies such as bleeding, blistering, and the salts of mercury and antimony. This new school sought to use milder remedies, usually of vegetable origin, for the treatment of specific conditions.

Other References.—"The Pharmaceutical Recipe Book," published by the American Pharmaceutical Association, has appeared in three editions, in 1926, 1938, and 1943, respectively. It contains many useful formulas for preparations formerly official and still in wide use and many others of value to the pharmacist interested in the manufacture of side lines on a small scale.

Textbooks in Pharmacy.—There were textbooks upon the techniques and apparatus of pharmacy as early as the sixteenth century. Such texts were rather numerous in Germany and France in the seventeenth century, but England was no better off than the United States in this respect. Carl Friedrich Mohr, a German, was the first to describe the apparatus and manipulations pertaining to the profession. His book "Lehrbuch der Pharmazeutischen Technik," published in 1847, filled a great need in England and America. It was soon translated into English by Theophilus Redwood for use in Great Britain. In 1849, William Procter, Jr., issued an extended edition of Redwood's translation, making it a useful book for students of pharmacy in America. It was a practical text and described and explained most of the fundamental procedures. However, it was never revised. The fact that English-speaking pharmacists had no textbook upon the subject of pharmacy until about a century ago indicates something of the educational status of the profession at that time.

The first truly American textbook dealing with the profession was published by Edward Parrish in 1855. It was entitled "Introduction to Practical Pharmacy" and was designed to be used as a text for medical students whom Parrish taught at a

private school of practical pharmacy. The second edition appeared in 1859 and the third in 1864, and at this time the title was changed to "A Treatise on Pharmacy." Parrish died in 1872, and Thomas Wiegand continued the book, publishing the fourth edition in 1874 and the fifth in 1884. Each edition became increasingly valuable as a text for pharmacists.

In 1885, the first edition of Remington's "The Practice of Pharmacy" appeared. The author carried it through five more editions, in 1889, 1894, 1905, 1907, and 1917, respectively. The seventh edition appeared in 1926 and the eighth in 1936, edited by Remington's friends and associates at the Philadelphia College of Pharmacy following his death in 1917. The book is voluminous because it contains most of the monographs of the Pharmacopoeia and the National Formulary, in addition to much other useful pharmaceutical information. It has been popular for a long time as a text and reference for students and pharmacists.

In 1887, Reinhold Rother published "The Beginnings in Pharmacy." This was a small handbook type of text, which was well received. The author died in 1889, and the book was not republished.

The "Handbook of Pharmacy" by Virgil Coblentz was a concise treatise on pharmacy. It appeared first in 1894, and the second edition was published a year later. It emphasized the chemical aspects of pharmacy but was not continued beyond the second edition.

A book that has been well received as a text in pharmacy is "Treatise on Pharmacy" by Charles Caspari, Jr., the first edition of which was published in 1895. The author carried the book through five editions, the fifth appearing in 1916 at about the time of his death. The book was revised in 1920, 1926, and again in 1939 by E. F. Kelly, former pupil and associate of Caspari at the University of Maryland College of Pharmacy. It is essentially a text for students beginning pharmacy and serves this purpose well because it is lucidly written and systematically arranged and offers explanations that are helpful.

Another of the textbooks in pharmacy is H. V. Arny's "Principles of Pharmacy." This was first published in 1909, the second and third editions appearing in 1917 and 1926, respectively.

The fourth edition appeared in 1937, with R. P. Fischelis as collaborator. The book consists of seven parts, four of which pertain to pharmacy and three to chemistry. It differs from other texts in that it has an extensive but not entirely up-to-date bibliography at the end of each chapter. This should encourage students to consult the original references for information upon many subjects of interest to pharmacists.

In 1917, E. A. Ruddiman published his "Pharmacy, Theoretical and Practical." It was revised and enlarged in 1926, but later revisions have not appeared. In 1931, I. V. S. Stanislaus published "A Textbook of Pharmacy," with chapters on pharmacology, dispensing, and jurisprudence.

In 1932, H. C. Washburn and C. J. Klemme published "Beginning Pharmacy." Part I is devoted to theoretical considerations and Part II to laboratory exercises. One of the most recent texts in pharmacy is "Fundamentals of Pharmacy" by W. H. Blome and C. H. Stocking, published in 1939. Part I pertains to the theoretical and Part II to the practical aspects of the subject.

Books on Dispensing and Prescription Practice.—With respect to the subject of pharmacy the books just described are of a general nature and designed to be of help to the beginner in pharmacy or to serve as a reference for the busy practitioner. In keeping with the rapid educational advance of the latter part of the nineteenth and the early part of the present century books in specialized fields of pharmacy began to appear. Such texts in the fields of chemistry and materia medica were already known.

The first of these books appeared in 1895. It was "The Art of Compounding," by W. L. Scoville, who carried the book through four revised editions in the years 1902, 1904, 1914, and 1927. The sixth edition was much enlarged in 1937, with J. L. Powers as collaborator. The seventh edition was revised by G. E. Crossen and J. L. Powers, in 1943, being completely rewritten and the former arrangement of chapters altered.

A second book of this kind was published in 1897 by E. A. Ruddiman and entitled "Incompatibilities in Prescriptions." This book has gone through five revisions appearing in 1900, 1908, 1917, 1925, and 1936, respectively. The 1936 edition was rewritten and reset with the assistance of A. B. Nichols.

An elementary treatise upon the subject of dispensing was published by J. H. Beal in 1908, entitled "Prescription Practice and Dispensing." A fourth text of this character was published in 1935 by W. J. Husa, entitled "Pharmaceutical Dispensing." The second edition, much enlarged, appeared in 1941.

These books have all had wide acceptance, the most popular one for a long time being Ruddiman's "Incompatibilities in Prescriptions." The title appealed to pharmacists because, in prescription work, incompatibilities are ever-present problems.

The fact that these books, although restricted largely to dispensing problems, have been widely used by pharmacists is indicative of the educational and technical progress which has been made in American pharmacy during the past six decades. With a rapidly changing materia medica, frequent revisions of such reference books is imperative.

Books on Materia Medica and Pharmacognosy.—Books on the subjects of materia medica and pharmacognosy in America have not been numerous. A few, however, are well known and widely used in schools of pharmacy. The first of these was published by John M. Maisch in 1882, entitled "The Manual of Organic Materia Medica." It was never revised. In 1894, L. E. Sayre published "Organic Materia Medica and Pharmacognosy," which was revised in 1899 with W. C. Stevens as collaborator. In 1896, D. M. R. Culbreth first published "A Manual of Materia Medica and Pharmacology." This was an extensive and informative book that went through six editions, the last being in 1917. Two books that proved to be extensive treatments and that were popular for a time were those published by Henry Kraemer in 1915. They were entitled "Applied Economic Botany" and "Scientific and Applied Pharmacognosy." The latter was revised by the author in 1920. The third revised edition appeared in 1928, published by an editorial board composed of E. L. Newcomb, L. K. Darbaker, E. B. Fischer, and E. N. Gathercoal.

A new textbook in pharmacognosy based upon the third edition of Kraemer's pharmacognosy was the text "Pharmacognosy" published in 1936 by E. N. Gathercoal and E. H. Wirth.

In 1914, H. W. Youngken first published "A Textbook of Pharmacognosy." This has gone through five revisions, the latest appearing in 1943. It is an extended and valuable text.

The subject of pharmacognosy was given emphasis in a text entitled "Pharmacognosy and Materia Medica" by H. C. Washburn and W. H. Blome, published in 1927. This contained a chapter on vitamins and one on insulin by Walter Pitz.

A textbook entitled "Pharmaceutical Therapeutics" was first published by E. V. Lynn in 1928 and revised in 1938. This was written for use as a text in schools of pharmacy.

Books on Chemistry and Pharmaceutical Chemistry.—The data on early textbooks on the subjects of chemistry and pharmaceutical chemistry are not only meager but scattered, it being thus almost impossible to form a complete idea of the development of this aspect of the literature. It would be interesting, if time and space permitted, to present the historic background of modern chemistry from its beginnings in Egypt and its survival through the long period of alchemy to the period of iatrochemistry of the later medical chemists. The latter served as the link between alchemy and modern chemistry. Modern pharmacy is rooted in the sciences of biology and chemistry. Pharmaceutical chemistry is a modern term which indicates that the science of chemistry has been adapted to the needs of pharmacy.

In this brief résumé of textbooks on chemistry the discussion will center on early American texts. Our early writers of texts on chemistry were physicians. Early American teachers of, and writers on, botany and materia medica were also usually physicians. The early American pharmacopoeias, including the Pharmacopoeia for several decades, were written by medical men. It has been stated that Dr. Benjamin Rush (1745–1813) was the first American to publish a book on chemistry. The date is given as 1770. James Woodhouse (1770–1809) was the first to write an experimental guide for students of chemistry. It was called "Young Chemists' Pocket Companion." John Gorham (1783–1829) wrote a treatise "The Elements of Chemical Science" that appeared in two volumes in 1819 and 1820.

In England, George Fownes (1815–1847) was the author of "Elementary Chemistry, Theoretical and Practical." The book was taken through several editions by R. Bridges; some of these were American editions, indicating its use here. A popular and widely used textbook on chemistry was "Chemistry, Medical

and Pharmaceutical" written by John Attfield, professor of chemistry for the Pharmaceutical Society of Great Britain. It was first published in 1867 in London. The first American edition appeared in 1870 and was written in response to the requests of interested friends in the United States.

In America, in 1881, John Uri Lloyd wrote his "Chemistry of Medicines." In 1884, Dr. William Simond first issued his "Manual of Chemistry." In 1886, E. H. Bartly published his "Textbook of Medical and Pharmaceutical Chemistry." Oscar Oldberg and J. H. Long published a "Laboratory Manual of Chemistry, General and Pharmaceutical" in 1887. In 1894, F. J. Wulling published "An Elementary Course in Inorganic Pharmaceutical Chemistry." The following year, 1895, S. P. Sadtler and H. Trimble published the first edition of their "Textbook of Chemistry for the Use of Pharmaceutical and Medical Students." This book has gone through six editions, the last being in 1927, edited by F. P. Stroup.

Books on Applied Chemistry and Qualitative and Quantitative Analysis.—The rapid advances that were made in chemistry in the last half of the nineteenth century are reflected in the textbooks that appeared on the subjects of assaying, organic analysis, qualitative and quantitative analysis, and other phases of applied chemistry. Many of these were written by teachers of chemistry in our schools of pharmacy and present problems of interest to the pharmaceutical chemist. A number of these are listed chronologically as follows:

1873 "Manual of Chemical Analysis as Applied to the Examination of Medicinal Chemicals" by Frederick Hoffmann.
1875 "Outlines of Proximate Organic Analysis" by A. B. Prescott.
1877 "Qualitative Chemical Analysis" by Prof. Douglas and A. B. Prescott.
1879 "First Book of Qualitative Chemistry" by A. B. Prescott.
1883 "Examination of Medicinal Chemicals" by Frederick Hoffmann and F. B. Powers.
1886 "Manual of Practical Assaying" by A. B. Lyon.
1886 "Practical and Analytical Chemistry" by H. Trimble.
1887 "Organic Analysis" by A. B. Prescott.
1889 "Lessons in Qualitative and Volumetric Chemical Analysis" by C. O. Curtman.
1890 "Uses, Tests for Purity and Preparation of Chemical Reagents" by C. O. Curtman.

1894 "Textbook of Volumetric Analysis" by H. W. Schimpf.
1899 "Handbook of Practical Assaying of Drugs and Galenicals" by A. B. Lyon.
1899 "A System of Instruction in Qualitative Chemical Analysis" by A. H. Elliott and G. A. Ferguson.
1901 "A Manual of Volumetric Analysis" by V. Coblentz. The second edition appeared in 1909 with A. Vorisek as collaborator.
1903 "Essentials of Volumetric Analysis" by H. W. Schimpf. The text was revised in 1909, 1911, and 1917.
1905 "A Systematic Course of Qualitative Chemical Analysis" by H. W. Schimpf. A. I. Cine was collaborator for the fourth edition.
1914 "A Laboratory Manual of Elementary Qualitative Chemical Analysis" by A. R. Bliss. This was revised several times, the fifth edition appearing in 1928, with H. H. Schaeffer as the senior author.
1920 "A Laboratory Manual of Qualitative Chemical Analysis" by T. J. Bradley. The book was carried through several editions.
1928 "Qualitative Analysis for Students of Pharmacy and Medicine" by C. B. Jordan. The second edition appeared in 1938, with H. G. DeKay as collaborator.
1930 "Qualitative Pharmaceutical Chemistry" by G. L. Jenkins and A. G. DuMez. The second edition was published in 1937.
1930 "Inorganic Pharmaceutical Chemistry" by Charles H. Rogers. The second edition appeared in 1936 and the third in 1943.
1941 "Organic Chemistry" by Eldin V. Lynn.
1941 "The Chemistry of Organic Medicinal Products" by Glenn L. Jenkins and Walter H. Hartung. The second edition appeared in 1943.

Books on the History of Pharmacy.—Books by American writers having to do with the history of medicine and the sciences are numerous, but texts on the history of pharmacy are few in number. Much pharmaceutical history, however, is to be found in books on the history of medicine, botany, and chemistry. For this reason it is necessary to include such titles in a list of references for the history of pharmacy.

The Historical Section of the American Pharmaceutical Association was organized in 1902 and has held sessions each year at the time of the annual convention of the association. During these years more than 500 papers upon various phases of historical pharmacy have been presented before the section. A number of these have been published, but the great amount of information that is available in such a list of papers lies buried in the archives of the association to be made available, we hope, by able historians of the future.

"The Pharmaceutical Syllabus" (tentative fifth edition) outlines the course of the history of pharmacy in considerable detail. Included, also, are outlines for the ethics and literature of pharmacy. To give serious study to these three subjects in one course is no small task, but they are all deserving of attention in a modern curriculum dealing with the study of pharmacy.

In the *Journal of the American Pharmaceutical Association* for 1936 to 1939 are to be found lists of texts on the history of pharmacy that should be helpful to students.[1] A selected list of these references is given here in chronological order, with the author, title, and publisher. In some cases this information is not complete. A brief comment or statement is given relative to each text.

PAREIRA, J. "The Elements of Materia Medica and Therapeutics," 3d American ed., Vol. 1 (1852), Vol. 2 (1854), edited by Joseph Carson. These volumes have been referred to as an encyclopedia of materia medica.

PHILLIPPE, A. "Histoire des apothicaires," 1853. The book is written by a physician and is the first attempt at writing a history of pharmacy.

LUDWIG, H. "Geschichte der Apotheker," 1858. Ludwig's book of 1,122 pages contains extensive data on the outstanding pharmacists in Europe over a period of six centuries.

BELL, J., and T. REDWOOD. "Historical Sketch of the Progress of Pharmacy in Great Britain," 1880. The first part of the book was written in 1842 by Jacob Bell. Theophilus Redwood's long period of constructive pharmaceutical service makes it authoritative for British pharmacy. Copies are still available.

PETERS, H. "Pictorial History of Ancient Pharmacy," 1899. Translated from the German by William Netter. The book is out of print, but copies may still be available. It is very readable and well illustrated.

ANDRÉ-PONTIER. "Histoire de la pharmacie, moyen age, temps moderne," 1900. This book of 729 pages is devoted largely to the history of French pharmacy.

SCHELENZ, H. "Geschichte der Pharmazie," 1904. This is a standard work of 935 pages and is in some respects the most comprehensive treatise upon the subject. It is really not a history but an encyclopedia on innumerable subjects pertaining to pharmacy and is valuable as a reference.

BARRETT, C. R. B. "History of the Society of the Apothecaries," 1905. A detailed history of the Society of the Apothecaries from 1617 to 1780.

[1] *J. Am. Pharm. Assoc.* **25**, 1172 (1936); **26**, 1106 (1937); **27**, 1118 (1938); **28**, 923 (1939).

"Half a Hundred Years of Development," *Druggists' Circ.* 51, 1–194 (January, 1907). To celebrate their Golden Jubilee the *Druggists' Circular* for January, 1907, was dedicated to the history of pharmacy in America. There are many interesting papers upon all phases of American pharmacy in this issue. Pictures of many illustrious pharmacists of the period are included.

WOOTTON, A. C. "Chronicles of Pharmacy," 1910. A good reference in two volumes, with fine illustrations.

KELLY, H. A. "Some American Medical Botanists," 1914. The book contains interesting sketches of some of our great medical botanists.

KREMERS, E. "Bibliographical Guide for the Students of the History of Pharmacy," 1916.

BRUNTZ, L., and M. JALOUX. "Plantes officinales," 1918. It is not so indicated in the title but there is a valuable general account of the pharmacopoeias of the world up to the time the book was published.

FALCK, A. "Die Arzneibücher," 1920. This book gives an extended account of the pharmacopoeias of the world.

ENGLAND, J. W. "The First Century of the Philadelphia College of Pharmacy, 1821–1921," 1922. A detailed history of America's first college of pharmacy. A supplement for the years 1921–1931 is also available.

RAUBENHEIMER, O. "Early History of Pharmacy of America." This is a short history of 21 pages that appeared in the pharmacy number of *Medical Life* **33** (No. 2), (1926).

LAWALL, C. H. "Four Thousand Years of Pharmacy," 1927. An interesting book but in no sense a history text. It is illustrated.

SARTON, G. "Introduction to the History of Science," Vol. I, 1927. This and succeeding volumes constitute a helpful reference book on the history of the sciences.

URDANG, G. "Wesen und Bedeutung der Geschichte der Pharmazie," 1927. This booklet of 41 pages discusses the importance of the history of pharmacy.

"Plough Court—The Story of a Notable Pharmacy," 1927. The book gives an interesting history of the old Plough Court Pharmacy in London. It is well illustrated and documented. The story in no way pertains to American pharmacy; yet it portrays the development of a pharmaceutical house that is known throughout the world and hence is of great interest.

SINGER, C. "From Magic to Science," 1928. English herbals, magic, and science are discussed in an interesting and readable manner. There are 108 figures and 14 colored plates.

WIMMER, C. P. "The College of Pharmacy of the City of New York—A History," 1929. An intimate history of the college.

THOMPSON, C. J. S. "The Mystery and Art of the Apothecary," 1929. This is an invaluable and interesting book written by an author in the field.

"Revue d' histoire de la pharmacie" is issued as the *Bulletin de la Societé d' histoire de la pharmacie.* Volumes 1, 2, and 3 appeared in 1930, 1931, and 1932, respectively. Later volumes have been published also.

STUBBS, S. G. B., and E. W. BLIGH. "Sixty Centuries of Health and Physic," 1931. This is a valuable reference book. It contains an interesting account of health, disease, and superstitions from ancient to modern times. It is illustrated with plates and is well documented.

BLANTON, W. B. "Medicine in Virginia in the Eighteenth Century," 1931. Chapter 3 is an interesting account of early pharmacies and the drug business in America.

DE ROSEMONT, L. R. "Histoire de la pharmacie a travers les âges," 1931. This is a work of 1,266 pages in two volumes and is perhaps the best general history of pharmacy published in France.

ADLUNG, P. A., and G. URDANG. "Grundriss der Geschichte der deutschen Pharmazie," 1935. This treatise of 647 pages is a general history of pharmacy in Germany and should be of value to teachers of the subject.

GRIER, J. "A History of Pharmacy," 1937. A history of ancient medicine, alchemy, herbal remedies, animal drugs, and modern pharmacy in Great Britain.

ARBER, A. "Herbals, Their Origin and Evolution," A Chapter in the History of Botany 1470–1670, 1938. The book is well written and interestingly illustrated.

ORNSTEIN, M. "The Role of the Scientific Societies in the Seventeenth Century," 1938. A treatise on the learned societies, colleges, and journals of Europe and England. An earlier edition was published in 1913.

KREMERS, E., and G. URDANG. "History of Pharmacy," 1940. This first real American text on the history of pharmacy is excellent as a guide and a survey. To read it is to become convinced that pharmacy is a profession and deserves to be considered an ancient and honorable calling. Every pharmacist should read it.

COOPER, J. W. "Tutorial Pharmacy," 3d ed., 1941. The first 39 pages are devoted to the History of Pharmaceutists, and Chap. 31 is an Outline of the Development of Bacteriology.

Journals of Pharmacy.—An interesting phase of the history of American pharmacy is to be found in a study of the pharmaceutical journals. Numerically speaking, the United States has had more than its share of journals devoted to, or of interest to, pharmacy but as to their quality one might raise many questions.

The *American Journal of Pharmaceutical Education* for April, 1943, contains a list of more than 500 titles of pharmaceutical journals of which the majority are American.

This list shows that many of the journals went through various changes in titles and numerous consolidations. An even larger

number ceased to exist after a few years or, in a few cases, within a few months. Though so many pharmaceutical journals were short-lived, there still remains a list that is entirely too long, most of which are trade journals of local or otherwise restricted interest.

It is an interesting historical fact that the appearance of these many journals coincided with other developments in American pharmacy such as the growth of schools and colleges, state associations, state laws governing the practice of pharmacy, and state boards of pharmacy. These developments are evidence of a rapidly growing profession in a country that extended its frontiers westward within the short period of a few decades. It would seem, therefore, that the great number and variety of pharmaceutical journals reflect the pharmaceutical response to the changing social, economic, and political conditions which were to be found in the United States following the Civil War.

It is not an easy task to evaluate the many journals in pharmacy. For the most part, they represent trade interests, and these interests are not much concerned about the nature and character of pharmaceutical publications inasmuch as they are primarily motivated by the ways and means of advertising. Conversely, professional pharmacists and pharmaceutical educators are not, as a rule, interested in trade journals, and the situation remains unimproved. In fact, several of the older semiprofessional journals that used to furnish good reading for practicing pharmacists have, in recent years, become more sensational and less valuable.

In 1940, Ellsworth[1] made an interesting study of the journals of pharmacy. He had 114 journals evaluated by a group of pharmaceutical educators. In this list were journals on the subjects of chemistry, biology, and medicine as well as pharmacy. He writes,

> Trade journals do not appear in the top half. This should be heartening to those who believe that the fundamental chemical, biological, and medical disciplines should dominate education in pharmacy. Likewise, it shows that the trade journals do not rank high in the opinion of the professors of pharmacy.

[1] R. E. Ellsworth. "An Evaluation of Pharmacy Journals," *Am. J. Pharm. Education* **4**, 14–19 (1940).

He does not dismiss the problem but goes on to say,

The place of the trade journals in a pharmacy library would seem worthy of discussion. Some of these are purely commercial, serving as advertising media for all kinds of goods. Some professors argue that trade journals have no place in the library. Others maintain that they are needed for their negative values. In other words, the instructors can analyze and expose fallacious advertising for the students. Instructors who are interested in the problem of controlling the sale and use of quack remedies will need the trade magazines, both honest and unscrupulous. Their chief danger in a pharmacy list lies in their attractiveness, which will often seduce a student's attention and use his valuable time.

The reader is referred to this paper for details. It will be observed that the trade journals, some of which are widely distributed, are very low on the list. It might be enlightening to have other evaluations, especially from those practicing pharmacy.

Many years ago Rusby[1] wrote critically of the influence of pharmaceutical and medical journals upon materia medica. He referred to the past when it was not uncommon for physicians to be stockholders in companies that manufactured nostrums. He writes,

The influence of the medical and pharmaceutical journals upon these conditions should not be overlooked. With few exceptions, these agencies have led a dual life, the one represented in their editorial management, the other in their advertising pages. To criticisms, they reply that the reader is to look in the editorial portions for such principles as the journal espouses, and for such advice as it is disposed to give. Those who prefer to accept information and advice from the interested parties who advertise are to regard the advertising pages as so much space hired by the advertiser, for stating his case, for which the journal, as a moral agent, assumes no responsibility. Not only is this view incorrect and improper, but its influence and effect upon the materia medica have been unqualifiedly bad. Even if left to themselves, neither the lay nor the professional public will dissociate the influence of the jour.. .1 from that of its advertisements, and as a matter of fact, the journals usually endeavor to make themselves as useful as possible to

[1] H. H. Rusby. "Fifty years of Materia Medica," *Druggists' Circ.* **51**, 29–43 (1907).

dishonest advertisers. On the whole, it is not too much to say that the advertising of unworthy things in the medical and pharmaceutical journals has been one of the most potent influences in the corruption of materia medica.

Since Rusby wrote these lines the *Journal of the American Pharmaceutical Association* has appeared. Published monthly, it has been the organ of the American Pharmaceutical Association and has maintained an effective editorial and professional policy. Inasmuch as fewer than 5 per cent of the pharmacists of the country hold membership in the association, the influence of the journal, although very good, has not been extensive. In 1940 the name of this journal was changed to the *Journal of the American Pharmaceutical Association, Scientific Edition,* and a new monthly journal was created with the title *Journal of the American Pharmaceutical Association, Practical Pharmacy Edition.* This is especially designed to interest the pharmacists, and arrangements have been made with a number of the state associations to have their membership receive this new journal, offering an extended service by the offices of the Association located at Washington and help to the pharmacists of the country.

The *American Journal of Pharmaceutical Education* appeared first in 1936. It is published quarterly and is the organ of the American Association of Colleges of Pharmacy. While it is of primary interest to those in teaching, it should interest every professionally minded pharmacist. It reflects the high scholastic and professional standards of the leadership of American pharmacy to be found in our colleges of pharmacy.

An association journal of interest is the *Bulletin of National Association of Boards of Pharmacy.* It is published monthly at Chicago by the secretary of the association and carries news of interest to the members of the state boards of pharmacy.

The newspaper of American pharmacy is *Drug Topics,* published weekly in New York City by the Topics Publishing Co. It has the largest circulation perhaps of any of the pharmaceutical journals, being sent free to store owners. This is made possible by the extensive amount of advertising it carries.

The oldest journal of pharmacy in America is the *American Journal of Pharmacy,* which has been published by the Phila-

delphia College of Pharmacy since 1825. This journal has remained professional from the beginning. From its volumes can be obtained a continuous picture of American pharmacy not to be found elsewhere.

In 1857, the second oldest American journal of pharmacy was founded. It was called the *American Druggists' Circular and Chemical Gazette* and later became known as the *Druggists' Circular*. It consolidated with *Drug Topics* in 1940. In January, 1907, the *Druggists' Circular* issued a Golden Jubilee number that contains 194 pages of interesting accounts of persons and events in American pharmacy. A journal that is well known and widely read is the *National Association of Retail Druggists' Journal.* This is essentially a journal devoted to trade interests, but in recent years it has given attention to professional problems. It is published bimonthly at Chicago.

Several journals that were widely read a generation ago are no longer published. Among them were the *Pharmaceutical Era, Spatula,* and *Midland Druggist.* Among the older journals that still survive and have not yet been mentioned are the *American Druggist, Merck Report, Northwestern Druggist, Oil, Paint and Drug Reporter, Pacific Drug Review,* and *Southeastern Drug Journal.*

In 1933, Meyer[1] published a list of pharmaceutical journals by states. Naturally a larger number of these periodicals are to be found in those states which have large cities. This paper was published with the thought that those interested would report errors, omissions, etc., which would aid in drawing up a more nearly complete and correct list, but the response was not encouraging.

Some educators in the schools of pharmacy feel that journals are adjuncts to good teaching and think that students in pharmacy should know the better journals in the field. A good way to accomplish this is for teachers to assign a number of journal references for each student to read and report on. The attitude of editors and publishers of journals is not like that of educators. As a consequence, certain features in the journals result in

[1] M. Meyer. "The Pharmaceutical Journals of the United States," *J. Am. Pharm. Assoc.* **22**, 424–9 (1933).

inconvenience to teachers and students. In 1939, Lee[1] pointed out the weaknesses that, if corrected, would make many pharmaceutical journals more useful. This applies especially to the trade journals. Among other things it was stated that any number of journals (1) do not page consecutively through the volume and (2) do not publish an index for the volume, both of which make it difficult to locate articles in bound volumes. Earlier in this chapter it was suggested that these journals are essentially mediums of advertising. For this reason, the reading matter is often hard to find or at least is inconveniently placed. It is perhaps too much to expect such journals to serve well both the advertiser and the student. It will be observed that the most worth-while technical and professional literature is not obscured by advertisements. The excessive advertising that is carried by the trade journals certainly makes binding them for future use rather questionable. Perhaps such journals should be read for their current news and then discarded.

It is not necessary here to give the reader a detailed description of the journals. Every school of pharmacy should have a library accessible to the students, so that they may become familiar with current periodicals. Professional journals, even those representing trade interests, carry information about new items. Persons in the profession should read the journals in order to be informed, but it often happens that the long, busy hours required of pharmacists do not allow them sufficient time for productive reading. There are those who feel that the profession of pharmacy will improve only as those who are part of it become more professional in their attitude. This in turn will be reflected in the kind and amount of literature they read.

A selection for such study and use by students of pharmacy is given here. For each there is an abbreviation, the date of founding, the title or titles, consolidations and, if no longer published, the date it ceased to be published, and the city in which it is published. This constitutes a brief history of the journals. For a much more extensive list of journals devoted to pharmacy and its allied sciences, that prepared by the Committee on Libraries of the American Association of Colleges of Pharmacy

[1] C. O. Lee. "How the Pharmaceutical Journals Could Help the Teachers of Pharmacy," *Am. J. Pharm. Education* **4**, 24 (1939).

[*Am. J. Pharm. Education* **7**, 187–217 (1943)], the "List of Periodicals" abstracted by *Chemical Abstracts* (1936 and 1942), and the "Union List of Serials" should be consulted.

PHARMACEUTICAL JOURNALS, THEIR ABBREVIATIONS AND HISTORY

Am. Druggist
New Remedies, 1871–1883
American Druggist, 1884–1893
American Druggist and Pharmaceutical Record, 1893–1923
American Druggist, 1923——. New York
(Absorbed *Aromatics*, March, 1932)

Am. J. Pharm.
Journal Philadelphia College of Pharmacy, 1825–1835
American Journal of Pharmacy, 1835——. Philadelphia
(The journal contains some abstracts)

Am. J. Pharm. Education
American Journal on Pharmaceutical Education, 1937——. Lincoln, Neb.

Am. Perfumer
American Perfumer and Essential Oil Review, 1906–1936
American Perfumer, 1936–1940
American Perfumer and Essential Oil Review, 1940——. New York

Am. Professional Pharmacist
American Professional Pharmacist, 1935——. New York

Apoth.
New England Druggist, 1888–1903
Apothecary and New England Druggist, 1903–1904
Apothecary, 1904——. Boston

Arch. Pharm.
Archiv der Pharmazie, 1822–1832, united with *Magazin für Pharmazie* to form
Annalen der Pharmazie, 1832–1834
(The *Archiv der Pharmazie* separated from the *Annalen* in 1834)
Archiv der Pharmazie, 1835–1924
Archiv der Pharmazie und Berichte der deutschen pharmazeutischen Gesellschaft, 1924——. Berlin

Australasian J. Pharm.
Australasian Journal of Pharmacy, 1886——. Melbourne

Brit. Chem. Physiol. Abstracts
British Chemical Abstracts, 1926–1939
British Chemical and Physiological Abstracts, 1939——. London

Bull. Lloyd Library
Bulletin Lloyd Library, Botany, Pharmacy, and Materia Medica, 1902——. Cincinnati

Can. Pharm. J.
Canadian Pharmaceutical Journal, 1868——. Toronto

Chem. Abstracts
Chemical Abstracts, 1907——. Columbus
(Section 17 is devoted to pharmaceutical topics)
Chemist and Druggist
Chemist and Druggist, 1859——. London
Chem. Zentr.
Chemisches Zentralblatt, 1897——. Berlin. (Contains abstracts)
Deut. Apoth. Ztg.
Apotheker Zeitung, 1886–1933
Standeszeitung Deutscher Apotheker, 1933–1934
Deutsche Apotheker Zeitung, 1934——. Berlin
Drug Cosmetic Ind.
Weekly Drug Markets, 1914–1916
Drug and Chemical Markets, 1916–1926
Drug Markets, 1926–1932
Drug and Cosmetic Industry, 1932——. New York
Druggists' Circ.
American Druggists' Circular and Chemical Gazette, 1857–1866
Druggists' Circular and Chemical Gazette, 1866–1906
Druggists' Circular, 1907–1940. (Consolidated with *Drug Topics*, November, 1940) New York
Drug Topics
Drug Topics, 1883——. New York
Drug Trade Weekly
Drug Trade Weekly, 1918–1922, with *Pharmaceutical Era*, 1923–1928, again as
Drug Trade Weekly, 1928——. New York
Ephemeris Materia Med., Pharm., Therap., Squibb's
An Ephemeris of Materia Medica, Pharmacy, Therapeutics, and Collateral Information, Squibb's, 1882–1904. New York
El Farmaceutico
El Farmaceutico, in Spanish. New York
Indian Eastern Druggist
Indian and Eastern Druggist, 1920——. London
Interstate Druggist
Midland Druggist, 1899–1909
(Absorbed *Pharmaceutical Review and Pharmaceutical Archives*, 1909)
Midland Druggist and Pharmaceutical Review, 1909–1926.
Interstate Druggist, 1926——. Columbus, Ohio
J. Am. Pharm. Assoc.
Journal of the American Pharmaceutical Association, 1912–1940. Successor to the *Proceedings of the American Pharmaceutical Association*, 1852–1911, and the *Bulletin of the American Pharmaceutical Association*, 1906–1911
(The *Proceedings* of this organization contained abstracts)

J. Am. Pharm. Assoc. Practical Pharm. Ed.
Journal of the American Pharmaceutical Association Practical Pharmacy Edition, 1940——. Washington, D.C.
J. Am. Pharm. Assoc. Sci. Ed.
Journal of the American Pharmaceutical Association Scientific Edition, 1940——. Baltimore
J. pharm. chim.
Bulletin de pharmacie, 1809–1814
Journal de pharmacie et des sciences accessoires, 1815–1841
Journal de pharmacie et de chimie, 1842——. Paris
Liebig's Ann. Chem.
Magazin für Pharmazie und Experimental Kritik, 1823–1831
Annalen der Pharmazie, 1832–1842
Annalen der Chemie und Pharmazie, 1843–1872
Liebig's Annalen der Chemie, 1873——. Heidelberg
Merck Rept.
Merck's Monthly Report, 1892–1892
Merck's Market Report, 1892–1893
Merck's Market Report and Pharmaceutical Journal, 1893–1895
Merck Report, 1896——. New York
Mfg. Chemist
Manufacturing Chemist and Pharmaceutical, Cosmetic and Photographic Trade Journal, 1930–1932
Manufacturing Chemist and Pharmaceutical, Cosmetic, and Perfumery Trade Journal, 1932–1936
Manufacturing Chemist and Pharmaceutical and Fine Chemical Trade Journal, 1936——. London
N.A.B.P. Bull. (Natl. Assoc. Boards Pharm. Bull.)
National Association Boards of Pharmacy Bulletin, 1935——. Chicago
N.A.R.D.J. (Natl. Assoc. Retail Druggists' J.)
National Association Retail Druggists' Notes, 1902–1913
National Association Retail Druggists' Journal, 1913——. Chicago
Northwestern Druggist
Northwestern Druggist 1899——. St. Paul, Minn.
(Absorbed the *Wisconsin Druggist Exchange* in 1902 and the *Official Register* in 1927)
Oil, Paint Drug Reptr.
Oil, Paint and Drug Reporter, 1871——. New York
(Absorbed *New York Druggists' Price Current*, 1874
Absorbed *Drug, Paint, and Oil Trade*, 1875, Philadelphia
Absorbed *New York Drug Bulletin*, 1875
Absorbed *Soap Makers Journal*, 1882
Absorbed *Oil and Paint Review*, 1883
Absorbed *Weekly Drug News and Prices Current*, 1885
Absorbed *International Petroleum Reporter*, 1922)

Pacific Drug Rev.
Pacific Drug Review, 1888——. Portland, Ore.
Pharm. Abstracts
Pharmaceutical Abstracts, 1935——. Washington
Pharm. Acta Helv.
Pharmaceutical Acta Helvetiae, 1925——. Zurich
(Scientific supplement to *Schweizerische Apotheker-Zeitung*)
Pharm. Arch.
Pharmaceutical Archives, 1898–1903. Milwaukee
(Consolidated with *Midland Druggist and Pharmaceutical Review*, 1903)
Pharmaceutical Archives, 1936——. Madison, Wis.
Pharm. J.
Pharmaceutical Journal and Transactions, 1841–1895
Pharmaceutical Journal, 1895–1909
Pharmaceutical Journal and Pharmacist, 1909–1933
Pharmaceutical Journal, 1933——. London
Pharm. Rev.
Pharmazeutische Rundschau, 1883–1895
Pharmaceutical Review, 1896–1909
(Consolidated with *Midland Druggist*, 1909)
Midland Druggist and Pharmaceutical Review, 1909–1926
Interstate Druggist, 1926——. *q.v.* Columbus, Ohio
Pharm. Weekblad
Pharmaceutisch Weekblad, 1864——. Amsterdam
Pharm. Zentralhalle
Pharmazeutische Zentralhalle für Deutschland, 1859——. Dresden-Blasewitz
(Contains abstracts)
Quart. J. Pharm. Pharmacol.
Proceedings of the British Pharmaceutical Conference, 1864–1869
Year Book of Pharmacy and Transactions of the British Conference or *Year Book of Pharmacy*, 1870–1927
Quarterly Journal of Pharmacy, 1928–1929
Quarterly Journal of Pharmacy and Pharmacology, 1929——. London
(This quarterly contains abstracts)
Schweiz. Apoth. Ztg.
Schweizerische Apotheker-Zeitung, 1862——. Zurich
(*Journal suisse de pharmacie; Giornale svizzero di farmacia.*)
Scientia Pharm.
Scientia Pharmaceutica, 1933——. Vienna
Southeastern Drug J.
Dixie Pharmaceutical Journal, 1926–1928
(Combined with *Southeastern Drug Journal*, 1928)
Southeastern Drug Journal, 1926——. Atlanta
Southern Pharm. J.
Southern Pharmaceutical Journal, 1908——. Dallas

Squibb Abstract Bull.
Squibb Abstract Bulletin, 1928——. Brooklyn
Union pharm.
L'Union pharmaceutique, 1860——. Paris
(Contains abstracts)
Yearbook Am. Pharm. Assoc.
Yearbook of the American Pharmaceutical Association, 1912–1935. Baltimore
(Contains abstracts)

House Organs.—House organs are publications available to pharmacy and medicine and are issued by the manufacturing companies. They serve as mediums of advertising for the respective concerns and often carry papers, abstracts, or reviews of items of interest to the pharmacist and the physician. However, should pharmacists confine their reading to this type of journal they would not be informed of the trends in pharmacy as expressed in the activities of the colleges of pharmacy and the state, national, and related associations. The house organs have become more numerous in recent years and are sent free to the trade. They have limited current interest and value but play a minor role in the literature of professional pharmacy. Examples of these journals are *Tile and Till* published by Eli Lilly and Company; *Modern Pharmacy* by Parke, Davis and Company; and *What's New* by the Abbott Laboratories.

College Journals.—Several of the schools and colleges of pharmacy issue journals of various sorts, usually as student publications. These are of interest mostly to the students, alumni, and friends of the schools. Apparently, these have not had much influence in shaping professional policy; but since they are a medium for the expression of student opinion upon many subjects, they are of value.

Nonpharmaceutical Journals.—The modern, well-trained pharmacist should be informed in several fields of science related to pharmacy. These include chemistry, botany, pharmacognosy, bacteriology, physiology, and pharmacology. This makes it necessary for him to know the literature of these fields, including books as well as journals. For this reason a selected list of nonpharmaceutical journals is offered here as a supplement to the preceding list of journals of pharmacy.

Biochem. J.
Biochemical Journal, 1906. London
Biol. Abstracts
Biological Abstracts, 1926——. Philadelphia
J. Am. Chem. Soc.
Journal of the American Chemical Society, 1879——. Washington, D.C.
J. Am. Dental Assoc.
Journal of the American Dental Association, 1914——. Chicago
J. Am. Med. Assoc.
Journal of the American Medical Association, 1883——. Chicago
J. Am. Vet. Med. Assoc.
Journal of the American Veterinary Medical Association, 1877——. Chicago
J. Assoc. Official Agri. Chem.
Proceedings of the Association of Official Agricultural Chemists, 1884–1912
Journal of the Association of Official Agricultural Chemists, 1915——. Washington, D.C. (Suspended publication 1917–1919)
J. Biol. Chem.
Journal of Biological Chemistry, 1905——. Baltimore
J. Chem. Soc.
Proceedings of the Chemical Society, 1841–1843
Memoirs and Proceedings of the Chemical Society, 1841–1848
Quarterly Journal of the Chemical Society, 1849–1862
Journal of the Chemical Society, 1862——. London
J. Chem. Education
Journal of Chemical Education, 1924——. Chicago
Ind. Eng. Chem.
Journal of Industrial and Engineering Chemistry, 1909–1922
Industrial and Engineering Chemistry, 1923——. Washington, D.C. In three editions.
Lancet
The Lancet, 1823——. London

STUDY QUESTIONS

1. What is meant by the literature of a profession?

2. To what extent may it be said that pharmacopoeias are indicative of the progress of the medical and pharmaceutical science of a country?

3. Outline briefly the plans followed in formulating the first Pharmacopoeia of the United States of America.

4. Name the countries that had national pharmacopoeias before the United States.

5. What other terms are synonymous with the word *pharmacopoeia?*

6. Which of the pharmacopoeias were in use in early America?

7. Why were there two official Pharmacopoeias in this country in 1830?

8. State briefly how the Pharmacopoeia is revised.

9. When was the National Formulary first published, and why was it published?

10. Who owns, and who revises, the National Formulary?

11. Who owns, and who revises, the "Pharmaceutical Recipe Book"?

12. Name (*a*) the early American dispensatories, (*b*) the later American dispensatories.

13. Name the two earliest pharmacy textbooks used in America.

14. When, and by whom, were the first lectures upon the subject of pharmacy given in America?

15. A century or more ago, physicians were the lecturers in chemistry and materia medica. Explain why.

16. In 1869, the University of Michigan granted the Ph.C. (pharmaceutical chemist) degree for the first time. Upon what grounds was this justified?

17. What classes of journals of pharmacy are there? Give examples.

18. Name 10 of the most worth-while journals of pharmacy, and list them in the order of their value, numbering your first choice as (1), etc.

19. What is a house organ?

20. Name several nonpharmaceutical journals that are considered essential for pharmacists in training and in practice.

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BOLTON, H. C. "A Catalogue of Scientific and Technical Periodicals, 1665–1882," Smithsonian Institution, Washington, D.C., 1885; 2d ed., 1898.

BOLTON, H. C. "A Select Bibliography of Chemistry, 1492–1892," Smithsonian Institution, Washington, D.C., Section VII, Periodicals, pp. 1068–1164, 1893; first supplement, 1899; second supplement, 1904.

BRUNTZ, L., and M. JALOUX. "Plantes Officinales," Vigot Frères, Paris, 1918.

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FALCK, A. "Die Arzneibücher," J. A. Barth, Leipzig, 1920.

"Historical Introduction," "The Pharmaceutical Recipe Book," American Pharmaceutical Association, Washington, D.C., 3d ed., 1943, pp. ix–xiii.

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Pan American Sanitary Bureau, *Publication* 152, Washington, D.C., 1940.

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CHAPTER VII

METROLOGY

The term *metrology* is derived from the Greek word *metron*, meaning measure (combining form, *metro;* + *logy*, the science of). It is usually understood to mean the science of weights and measures, although it also may refer to systems of weights and measures or to a treatise dealing with this subject. A thorough knowledge of the several systems of weights and measures used in pharmacy, together with a sound understanding of the relationships existing among the various units, is of the utmost importance to the beginning student of pharmacy, and the task of memorizing these values is one of his first assignments.

Origin of Units of Measurement.—Space does not permit a detailed discussion of the origins of weights and measures. The student is referred to the textbooks listed in Appendix I for additional information on the history of their development. It is interesting to note that, just as our decimal system of counting is supposed to have originated from the use of the fingers of the two hands by primitive man, other parts of the body have been used in measuring distances. This idea is illustrated in the following examples: the **thumb** (1 in.); the **hand** (4 in.); the **span** (distance from the little finger to the end of the thumb, when the hand is extended, 9 in.); the **foot** (the length of the human foot, 12 in.); the **cubit** (length of the forearm, or the distance from the elbow to the extended middle finger, 18 in.); the **yard** (originally the girth of a man, 3 ft.); and the **fathom** (the reach, or the distance between the fingertips when the arms are extended at the sides, 6 ft.).

In very early times, the bulk of solid substances was measured in pinches, handfuls (*drachmae*), etc.; and when it was a question of weighing substances, it was natural to turn to familiar, widely distributed objects as units of weight. Thus in England, during the reign of Henry III in the year 1266, it was decreed

that " . . . an English penny called a sterling, round and without clipping, shall weigh thirty-two wheat corns from the midst of the ear, and twenty pence do make an ounce, and twelve ounces one pound, and eight pounds do make a gallon of wine, and eight gallons of wine do make a London bushel, which is the eighth part of a quarter."[1] Later, in 1321, it was provided "that three barley-corns, round and dry, shall make an inch, and twelve inches a foot."

In the practice of pharmacy, unfortunately, several systems for measuring are used. Not only is it necessary to know each of the systems or tables involved, but also it is important to know under what conditions each must be employed. Some idea of the number of tables required may be obtained from the following: The pharmacist must be thoroughly familiar with at least three systems of weight, the metric, the apothecaries', and the avoirdupois, and may even have occasion to use a fourth, the troy system. In the measurement of volumes of liquids, the United States fluid system, metric volume, and the table of common equivalents (household measurements) are absolutely essential. In addition, the British imperial system is sometimes required. Both the English and the metric systems are used for measuring extension.

The Metric System.—Although not the oldest of the systems to be considered, the metric is the one most easily learned since it is based upon the decimal system. In origin, the system is usually credited to the French statesman, Prince de Talleyrand, but historians are not in agreement on this point. According to one writer,[2] the French astronomer Jean Picard (in 1671) and the Dutch physicist Christian Huygens (in 1673) proposed a standard unit of length equivalent to the length of the swing of a pendulum that would complete its oscillation in 1 sec. at sea level on the forty-fifth degree of latitude. Some years prior to this, Sir Christopher Wren had advocated a unit based upon the oscillation of a pendulum that would complete its vibration in

[1] E. Fullerton Cook and Charles H. LaWall. "Remington's Practice of Pharmacy," J. B. Lippincott Company, Philadelphia, 8th ed., 1936, p. 27.

[2] George F. Kunz. "The Encyclopedia Americana," Americana Corp., New York, 1940, Vol. 18, p. 729.

½ sec. In 1670, the French mathematician Gabriel Mouton suggested a standard unit of length equivalent to 1 min. of the earth's circumference (the unit now used as the geographical mile) and which he subdivided into decimal fractions, to which names of Latin origin were assigned. Despite these early beginnings, nearly a century elapsed before the idea of applying the decimal system to weights and measures was considered further. The Scottish inventor of the steam engine, James Watt (1736–1819), proposed a still closer approximation of the metric system, in which he selected as a unit of mass a definite volume of water and provided a simple interrelation of the units of length, area, volume, and mass; this proposal was communicated to Talleyrand.

In March, 1790, Talleyrand and Prieur des Vernois proposed to the French National Assembly that that body should undertake the study of a new system of weights and measures. After the assembly had referred the matter to the Committee on Agriculture for preliminary consideration, this body published, on Aug. 22, a decree sanctioned by Louis XVI that provided for the establishment of the new system, assigned to the Académie des sciences the task of determining the standard unit, and invited representatives of other nations to participate in this work. With the collaboration of representatives from Spain, Italy, Denmark, the Netherlands, and Switzerland in the discussion of the plan, the Académie des sciences appointed a committee composed of the scientists Borda, Lagrange, Lavoisier, Tillet, and Condorcet, who made their report to the assembly on Oct. 27, 1790. Since additional data were required, a second committee, in which Laplace and Monge replaced Lavoisier and Tillet, was appointed. On Mar. 19, 1791, this second committee recommended the adoption of the one ten-millionth part of the quadrant of the terrestrial meridian as the standard unit of length. This report was adopted by the assembly on Mar. 26, 1791, and five separate commissions were established to continue the study and submit necessary data. On Aug. 1, 1793, a decree was passed by the convention to the effect that the new system should be declared obligatory at the end of the year. However, unavoidable delays in the measurement of the earth's quadrant required further postponement, and it was not until

the decree of 18 Germinal, *An* III (Apr. 7, 1795) that the values for the various units were established. As a first step in the enforcement of the use of the new system, the decree of Sept. 23, 1795, required its use in the Commune of Paris. Despite this fact, there was a marked tendency for the people to cling to the older and more familiar systems of weights and measures. Therefore, in 1837, a law was passed that made the use in France of systems other than the metric system illegal after Jan. 1, 1840. Belgium, Holland, and Greece were among the first countries to adopt the system, and before the close of the nineteenth century it had become the legal standard in 40 nations and had achieved world-wide recognition in science. Although its use is not compulsory in Great Britain and the United States, it has been legal in the latter country since 1866. It is required that the metric system shall be used exclusively in the medical departments of the United States Army and the United States Navy, the United States Public Health Service, and the Marine Hospital Service. It is also taught exclusively in most of the medical schools of this country. As mentioned above, it finds almost universal use in the field of scientific research and is the system used by all modern pharmacopoeias.

Metric Length.—As a primary standard upon which the system is based, one ten-millionth of the earth's quadrant (when measured through the poles) was taken and named the **meter** (French *mètre*). Although this is the theoretical standard, the actual standard is the length of the platinum-iridium meter bar deposited in the **International Bureau of Weights and Measures** located at Paris, France. A replica of this prototype standard is in the custody of the **Bureau of Standards** at Washington, D.C. The length of the meter, in units that are more familiar to English-speaking people, is 39.3704 in. The meter is the primary standard from which all other units, whether for linear measurements, area, volume, or weight, are derived, either directly or indirectly. For the purpose of deriving a unit of volume, the tenth part of the meter (called the decimeter) was cubed, and this was named the **liter** (French—*litre*). In the more familiar English system, this is the volume, or capacity, of a cube measuring 3.937 in. on each side. The unit of weight, called the **gram** (French—*gramme*) was defined as the weight of

the thousandth part of a liter (which is equal to the cube of the hundredth part of the meter, or centimeter) of distilled water at a temperature of 4°C. This specific temperature was selected because water attains its maximum density at this point.

Multiples of the several units are indicated by the use of the prefixes *Deka-*, 10; *Hecto-*, 100; *Kilo-*, 1,000; and *Myria-*, 10,000. Decimal fractions are shown by the prefixes *deci-*, $\frac{1}{10}$; *centi*, $\frac{1}{100}$; and *milli-*, 1/1,000. In ordinary use, abbreviations are more commonly employed than the full names of the units. It should be noted that, in writing both the abbreviations and the names, the initial letter is usually capitalized if the value of the denomination is equal to one or more times the unit named in the suffix, but the initial letter is lower case if the denomination is a fractional part of the unit indicated by the suffix. This is done to avoid confusion, since the prefixes *Deka-* and *deci-* both begin with the letter **d**, and the prefixes *Myria-* and *milli-* both begin with the letter **m**.

TABLE II.—METRIC LENGTH

Measurement	Abbreviation	Equivalent
1 Myriameter	Mm.	10,000.0 M.
1 Kilometer	Km.	1,000.0 M.
1 Hectometer	Hm.	100.0 M.
1 Dekameter	Dm.	10.0 M.
1 Meter	M.	1.0 M.
1 decimeter	dm.	0.1 M.
1 centimeter	cm.	0.01 M.
1 millimeter	mm.	0.001 M.

In practice, the prefixes *Myria-*, *Hecto-*, and *Deka-* are rarely used, and the prefix *deci-* is encountered infrequently. On the other hand, the prefixes *Kilo-*, *centi-*, and *milli-* are commonly used.

For extremely small measurements, the units of the metric system have been further subdivided. A unit commonly employed in biology is known as the **micron** (μ), which is defined as the thousandth part of the millimeter. For smaller measurements, especially in physics for measuring the length of light waves, the **millimicron**, also known as the **micro-**

millimeter (mμ), is used. This unit is equivalent to the thousandth part of the micron. A still smaller unit is the **micromicron** (μμ), which is equivalent to the millionth part of the micron. Intermediate in value between the millimicron and the micromicron is the angstrom unit (A.U.), which is the unit most commonly employed in measuring the length of light waves and is equivalent to one ten-thousandth of the micron, or one-tenth of the millimicron.

Metric Volume.—In most pharmaceutical and chemical literature the term **cubic centimeter** (cc.) has largely replaced the term **milliliter.** Theoretically, these terms should be synonymous, since the liter is defined as one cubic decimeter, and the thousandth part of this, the milliliter, should be one cubic centimeter. However, in practice, graduates and other containers used to measure volumes of liquids are graduated, as, for example, in the case of the liter size, by marking the upper limit of the space occupied by 1 Kg. of distilled water weighed at 4°C. in vacuum, rather than by attempting to employ linear measurements to determine its volume. Careful determination shows that this procedure introduces a slight error, so that 1 ml. is actually 1.000027 cc. This difference is so small that for practical applications it may be ignored, and it is customary to use the two terms interchangeably.

TABLE III.—METRIC VOLUME

Measurement	Abbreviation	Equivalent
1 Myrialiter	Ml.	10,000.0 L.
1 Kiloliter	Kl.	1,000.0 L.
1 Hectoliter	Hl.	100.0 L.
1 Dekaliter	Dl.	10.0 L.
1 liter	L.	1.0 L.
1 deciliter	dl.	0.1 L.
1 centiliter	cl.	0.01 L.
1 milliliter	ml.	0.001 L.

In the use of the table for metric volume, the terms *liter* and *cubic centimeter* are most commonly employed, while the names of the other units are rarely mentioned. Thus, it is customary to express almost any volume above 1,000 cc. in terms of liters

and cubic centimeters, while the smaller unit (cubic centimeter) is used for any desired quantity less than 1,000.

In the ninth revision of the Pharmacopoeia and the fourth edition of the National Formulary, the term *milliliter* and the abbreviation **mil** were adopted, but so much objection was raised, especially to the abbreviation selected, that the next Pharmacopoeial Convention authorized the return to the term previously used, the cubic centimeter. The chief objection to the use of the abbreviation **mil** was due to the fact that this term had been adopted, either as a unit for measuring the diameter of wires, being 1/1,000 in., or as a unit in the measurement of angles (the length of the chord subtending an arc representing 1/6,400 of a circle) commonly used in target designation in fire-control data in military training. There could be little objection made to the use of the term *milliliter* if the abbreviation **ml.** were adopted.

Metric Weight.—The definition of the standard unit for metric weight (the gram) as the weight of 1 cc. of distilled water at 4°C. has been given above. As indicated there, 4°C. was selected because water attains its maximum density at this particular temperature. The table for metric weight follows.

TABLE IV.—METRIC WEIGHT

Measurement	Abbreviation	Equivalent
1 Myriagram	Mg.	10,000.0 Gm.
1 Kilogram	Kg.	1,000.0 Gm.
1 Hectogram	Hg.	100.0 Gm.
1 Dekagram	Dg.	10.0 Gm.
1 gram	Gm.	1.0 Gm.
1 decigram	dg.	0.1 Gm.
1 centigram	cg.	0.01 Gm.
1 milligram	mg.	0.001 Gm.

Mention should be made of the fact that in chemical literature the abbreviation **g.** is used for the gram. In pharmaceutical literature this abbreviation is usually avoided, and **Gm.** is used because of the danger of confusing the abbreviation for gram with that for grain. In both chemical and pharmaceutical work, the only units and abbreviations commonly used are those of

the kilogram, gram, and milligram. Although the other units are parts of the official table of metric weight, they have gradually fallen into disuse.

After one has become familiar with the several systems of weights and measures used in pharmacy, any discussion of the advantages of the metric system over the other systems may seem superfluous. The simplicity of the metric system, the uniformity of the relationship of each unit to the next higher unit in the system, and the ease with which calculations involving fractions can be made are at once apparent. It is possible to make all kinds of calculations involving addition, subtraction, multiplication, and division without wasting the time for conversions to common units that is required for all other systems. Another argument advanced for the adoption of the metric system for exclusive use in this country is the distinct advantage that we should gain in foreign trade, since, outside of this country and Great Britain, it is used almost universally. Great savings of time would be made by the clerks and draftsmen in engineering and surveyor's offices if the systems now in use were abandoned. Since the metric system is based upon the decimal relationship, there is much less chance for error in calculations involving quantities expressed in this system. It is hoped that the day will soon come when all other systems may be abandoned and the metric system will be used exclusively in pharmacy.

Weight and Mass.—The term **weight** signifies the measure of the force with which a body is attracted to the earth by gravity. It is therefore the measure of a force acting upon a body, rather than of the quantity of **mass** that the body contains. On the other hand, mass is a measure of the quantity of matter in a body as determined by comparing the changes in velocity that result when the body impinges upon a standard body. As ordinarily determined, it is assumed that the quantity of mass in a body is unvarying in amount and independent of its physical state, environment, or motion, although more recent investigations[1] tend to show that at extremely high velocities the mass of a body may depend slightly upon its velocity. According to Newton's law of universal gravitation, every material object in

[1] N. H. BLACK. "An Introductory Course in College Physics," The Macmillan Company, New York, 1935, p. 161.

the universe attracts, and is attracted by, every other material object. In general, the attraction between any two bodies is proportional to the mass in each of them and inversely proportional to the square of the distance between them.

Since weight is a measurement of the force of gravity, it follows that given objects may show slightly different weights at different locations on the surface of the earth. Theoretically, a given mass would have no weight at the exact center of the earth, since it would be attracted equally in all directions. If the same mass could be taken far enough out into space, its weight would become negligible, since the attraction between the earth and the object is proportional to the mass in each and inversely proportional to the square of the distance between them. Because of the fact that the earth is slightly flattened at the poles, a given object shows a slightly greater weight at the poles than at the equator, since it is nearer the center of gravity of the earth. According to Arny and Fischelis,[1] a body that shows a weight of 192 lb. at the poles would be attracted by a force of about 191 lb. at the equator. Again the altitude at the location where the weighing is made may have a slight influence upon the result. Another factor that is of considerably less importance but that nevertheless contributes slightly to the increase in gravitational force as the poles are approached is the decrease in centrifugal force induced by the earth's rotation. At the poles, the effect of centrifugal force is completely neutralized, while it attains its maximum at the equator.

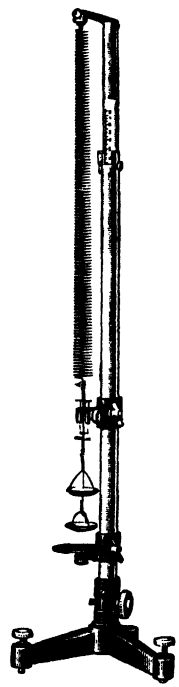


FIG. 2.—Jolly spiral balance.

It should be kept in mind that the variations in weight because of differences in location on the earth's surface can be observed only if a certain type of scale, such as the spiral-spring type (the Jolly spiral balance), is used. This instrument in Fig. 2 measures directly the pull of gravity. If an equal-arm balance

[1] H. V. ARNY and R. P. FISCHELIS. "Principles of Pharmacy," W. B. Saunders Company, Philadelphia, 4th ed., 1937, p. 39.

were used, two objects of equal mass would always be in equilibrium regardless of the altitude or latitude, since changes in the force of gravity would be the same with respect to the object being weighed and the standard weight used to counterbalance it. Actually, the weight of a body is equal to its mass, multiplied by the acceleration due to gravity at the place where the body is situated.

Troy Weight.—Although the troy system is not used in pharmacy, it is of historical interest because it is believed that apothecaries' weight is derived from it. This system, which takes its name from the important commercial center of Troyes, France, is the standard used in English-speaking countries for transactions involving gold and silver and other precious metals. It became well known in England during the fourteenth and fifteenth centuries and in 1527 replaced the Tower pound (5,400 gr.) as the legal mint standard. Since the apothecaries' pound and ounce have the same values (*i.e.*, contain the same number of grains) as those of the troy system, it may be assumed that the apothecaries' system is derived from the troy system. It is appropriate to indicate at this point that the troy grain, the apothecaries' grain, and the avoirdupois grain are identical in value and that the number of grains in a given system affords an accurate basis for conversion into appropriate units of any of the three systems.

TABLE V.—TROY WEIGHT

Equivalent	Measurement	Abbreviation	Total grains
24 grains	1 pennyweight	dwt.	24
20 pennyweight	1 ounce	oz.	480
12 ounces	1 pound	lb.	5,760

The abbreviation **dwt.** for the pennyweight may need explanation. It is a contraction of **denarius weight.** The Latin word *denarius* means an ancient Roman coin, originally (268 B.C.) made of silver; it is this coin which is referred to in the New Testament as the penny. The word **ounce** is derived from the Latin word *uncia*, meaning one-twelfth and indicating one-twelfth of a pound. It should be noted that the abbreviation for the ounce, **oz.**, is identical with that for the avoirdupois ounce. It is possible to tell which kind of ounce is indicated by noting the nature of the substance being weighed or the kind of transaction involved, since the troy ounce is applied exclusively to the weight of precious metals. The abbreviation **lb.** is derived from the Latin word *libra*, which means pound.

Apothecaries' Weight.—As previously indicated, it is thought that the apothecaries' (apoth.) system is derived from the troy

system, since the values for the grain, the ounce, and the pound are identical for the two. The apothecaries' system is used only in prescription compounding.

TABLE VI.—APOTHECARIES' WEIGHT

Equivalent	Measurement	Abbreviation	Total grains
20 grains	1 scruple	℈	20
3 scruples	1 drachm	ʒ	60
8 drachms	1 ounce	℥	480
12 ounces	1 pound	lb.	5,760

In the use of the apothecaries' system in prescription writing, the symbol or abbreviation for the denomination precedes the quantity, which is expressed in Roman numerals.

Avoirdupois Weight.—The name of the avoirdupois (av.) system would seem to indicate, at first glance, that it is formed by combining the French verb *avoir*, meaning **to have,** and the old French noun *pois*, meaning **weight,** so that the name might be translated literally as "to have weight," but this is probably an erroneous assumption. The French word *avoir* is not only the infinitive form of the verb meaning "to have," but it is also used in the sense of a noun meaning "goods" or "possessions." Thus the term might be translated as "goods of weight," and this meaning would be more in keeping with the way in which the system is used. Avoirdupois weight is the legal standard in English-speaking countries for all transactions involving bulky articles of ordinary value, as distinguished from precious metals (troy system), precious stones (the *carat*, etc.), and drugs and medicines (apothecaries' system in prescriptions).

The avoirdupois system is of French origin but probably was an outgrowth of the earlier Roman system. It was introduced into England during the fourteenth century, during the reign of Edward III but was not defined by statute until 1485. Although the larger units, the hundredweight (**cwt.**), the long hundredweight (**l. cwt.,** 112 lb.), the ton (**tn.,** 2,000 lb.), and the long ton (**l. tn.,** 2,240 lb.), are a part of the system, they are rarely encountered in pharmacy and for that reason are omitted from the table given below. It should be mentioned that the official

table for avoirdupois weight also provides for a unit called a dram (dr.), not to be confused with the apothecaries' drachm. It is defined as the sixteenth part of the avoirdupois ounce and therefore contains 27 11/32 gr. Fortunately, this unit, *i.e.*, the avoirdupois drachm, is used rarely, if at all, and finds no application in pharmacy. In the commercial sale of small quantities of drugs and chemicals, it is customary to use simple fractional parts of the ounce, as ¼ or ⅛ oz.

TABLE VII.—AVOIRDUPOIS WEIGHT

Equivalent	Measurement	Abbreviation	Total grains
437½ grains	1 ounce	oz.	437½
16 ounces	1 pound	lb.	7,000

United States Fluid Measure.—This system, also called apothecaries' fluid measure, wine measure, and United States liquid measure, is derived from the old wine measure of England, which became obsolete in 1825. It is based upon the standard unit of 1 gallon, the volume represented by 231 cu. in. In its pharmaceutical applications, it is customary to omit the quart, although this unit is included in the official table. In prescription writing, the symbol or abbreviation indicating the denomination precedes, followed by the quantity, expressed in Roman numerals. Occasionally Latin terms or abbreviations are used. These are as follows: minim, *minimus;* fluidrachm, *fluidrachma;* fluidounce, *fluiduncia;* pint, *octarius* (O.), meaning one-eighth of a gallon; gallon, *congius* (Cong.).

TABLE VIII.—UNITED STATES FLUID SYSTEM

Equivalent	Measurement	Abbreviation	Total minims
60 minims (♏)	1 fluidrachm	f ʒ	60
8 fluidrachms	1 fluidounce	f ℥	480
16 fluidounces	1 pint	pt.	7,680
8 pints	1 gallon	gal.	61,440

In the United States fluid system, it should be noted that the minim is merely the sixtieth part of the fluidrachm and has no direct relationship to the drop (Latin, *gutta*). The assumption

that the minim and the drop are equivalent is sometimes made, although there is no basis for it. Such an interpretation introduces gross inaccuracies in prescription compounding. The use of the drop as a unit of measurement for liquids will be considered later (page 183) under the discussion of Standard Droppers.

Table of Approximate Measures (Common Measures, Household Units).—Although this system has no legal status, it is a common practice in prescription dispensing to give directions on the label of liquid preparations that will be intelligible to the layman. Since he is not familiar with the units of the United States fluid system or the metric system, recourse is taken of the usual household utensils with which he is familiar, such as the various sizes of spoons, the wineglass, or the teacup. This system, while recognized by the tenth revision of the Pharmacopoeia, was not given official sanction in the later revisions. However, it continues to be used and must therefore be understood by the pharmacist.

TABLE IX.—APPROXIMATE MEASURES

Measurement	Metric	United States fluid system
1 teaspoonful	4 cc.	1 f℥
1 dessertspoonful	8 cc.	2 f℥
1 tablespoonful	15 cc.	4 f℥
1 wineglassful	60 cc.	2 f℥
1 teacupful	120 cc.	4 f℥
1 tumblerful	240 cc.	8 f℥

Considerable objection to the use of this system has been raised, since many investigators have reported that the usual types of household container listed in the table do not approximate the values assigned to them but tend to exceed them, in some cases by as much as 20 to 25 per cent.[1–5] Such inaccuracies in the administration of liquids largely offset the efforts of the prescribing physician and the dispensing pharmacist to attain

[1] M. I. WILBERT. *Am. J. Pharm.* **74**, 218 (1902).
[2] H. V. ARNY. *J. Am. Pharm. Assoc.* **6**, 1056 (1917).
[3] J. L. ADAMS. *Bull. Pharm.* **38**, 17 (1924).
[4] F. W. NITARDY. *J. Am. Pharm. Assoc.* **23**, 813 (1934).
[5] W. L. SCOVILLE. *Ibid., Practical Pharm. Ed.* **1**, 228 (1940).

accuracy and uniformity in dosage. It therefore becomes the duty of the pharmacist to discourage the use of such inaccurate measures and to urge that accurately graduated medicine glasses, which are readily available, shall be included in the equipment of the medicine cabinet of every home. Many progressive professional pharmacies have adopted the commendable practice of distributing standard spoons with all liquid prescriptions intended for internal use. Such spoons, made of molded plastic materials in attractive forms, are now available at a reasonable cost. This added service tends to emphasize the interest of the pharmacist in ensuring accurate dosage.

It should be noted that the metric equivalents in the table are only approximate values, representing the nearest whole number of cubic centimeters. As a result, the calculation of dosage based upon metric equivalents may lead to results slightly different from those obtained through the use of the equivalents of the United States fluid system. For this reason, the use of the United States fluid-system equivalents is recommended for all dosage calculations.

The British Imperial System.—Although this system has no legal status in this country, American pharmacists located near the Canadian border frequently have occasion to make use of it in the compounding of prescriptions written by Canadian physicians. Although the names of the denominations are exactly the same as those of the United States fluid system, it should be noted that no two of them coincide in value. Thus the pharmacist

TABLE X.—BRITISH IMPERIAL SYSTEM

Equivalent	Measurement	Abbreviation	Total minims
60 minims (♏)	1 fluidrachm	f℥	60
8 fluidrachms	1 fluidounce	f℥	480
20 fluidounces	1 pint	pt.	9,600
8 pints	1 gallon	gal.	76,800

who wishes to compound both American and Canadian prescriptions must have two entirely distinct sets of graduates and other measuring devices at hand, one for the United States fluid system and one for the British imperial system.

The standard unit of the British imperial system is the gallon, which is defined as the volume occupied by 10 lb. (av.) of distilled water weighed against brass weights at a temperature of 62°F. and at a barometric pressure

of 30 in. of mercury. The imperial standard gallon measure is a cylindrical brass vessel having a capacity of 277.420 cu. in. and a diameter equal to its height.

A comparison of this system with the United States fluid system can be made only by referring to the capacities of the gallons, as expressed in cubic inches. The British imperial gallon contains 277.420 cu. in., while the United States fluid gallon contains 231 cu. in. Division shows that one British imperial gallon is equivalent to 1.20094 United States fluid gallons.

Applications of the Various Systems of Weights and Measures. Since the British imperial system completes the list of tables of weights and measures that must be memorized, it is appropriate at this time to discuss briefly the uses and applications of the various systems. In commercial transactions involving drugs and chemicals in solid form (not in prescriptions), the legal standard is the avoirdupois weight system. However, the metric system may be used on an optional basis since it has been recognized in this country since 1866. As previously indicated, the troy system is used exclusively in this country for weighing precious metals such as gold and silver. In the writing of prescriptions the physician makes use of the apothecaries' weight system or the metric system. For liquid substances he employs the United States fluid system or the metric system of volume. Thus, in the compounding of prescriptions, a pharmacist may have to calculate costs on the basis of the price per avoirdupois pound and the selling price on the basis of the apothecaries' pound. He may also have to compute the price per fluidounce for liquids that he purchases on the basis of the avoirdupois pound. These calculations require a ready knowledge of the various systems and the equivalents used in making conversions.

List of Fundamental Equivalents.—In order to understand the relationships that exist among the units of the various systems, it is necessary to know certain factors that are used in making conversions. Some textbooks on pharmacy are subject to criticism in that they fail to distinguish between primary and secondary equivalents, with the result that so many equivalents are listed that the student becomes confused. Insofar as conversions of units of weight and volume are concerned, the most important thing is a complete knowledge of the tables of weights and measures and an understanding of the way in which the standard unit of each system is derived. In addition, there

are five conversion factors that must be memorized. With the exception of conversions dealing with linear measurements, all other conversion factors are of secondary importance and may be derived, when needed, from the tables and the primary equivalents that are listed below. These equivalents are as follows:

TABLE XI.—FUNDAMENTAL EQUIVALENTS

1 gram	= 15.432 grains
1 grain	= 0.065 gram
1 fluidounce	= 29.57 cubic centimeters
1 cubic centimeter	= 16.23 minims

1 fluidounce of distilled water, at 25°C., weighs 454.6 grains

As a corollary to the last equivalent, it should also be remembered that the gram is defined as the weight of 1 cc. of distilled water at 4°C. Since the standard working temperature of the Pharmacopoeia is 25°C., this means that 1 cc. of water weighs slightly less than 1 Gm. at this temperature. It is customary in practical applications to ignore this slight difference. Therefore, it can be assumed that, if 1 f℥ measures 29.57 cc., 1 f℥ of distilled water would weigh 29.57 Gm. Perhaps mention should be made of the fact that the twelfth revision of the Pharmacopoeia contains tables on Weight and Volume Relations (page 813) and Equivalents of Weights and Measures, Metric Avoirdupois and Apothecaries' (page 815). Numerous other tables of conversion factors are to be found in textbooks, handbooks, and other references, but the student should be warned against the too frequent use of such aids as this practice tends to impair his working knowledge of the tables and the primary conversion factors. In practice, it is customary to use approximate, or round, numbers rather than the exact equivalents. For example, 1 Gm. is commonly considered equivalent to 15 gr. and 1 f℥ to 30 cc. It should be pointed out that, in the compounding of formulas and the dispensing of prescriptions, no error is introduced if the same equivalent is used throughout, since the proportions remain fixed.

Conversions of Weights and Measures.—In the conversion of quantities of weights and measures expressed in one system to the proper units of another, the following may be encountered:

1. From metric weight to apothecaries' weight.
2. From metric weight to avoirdupois weight.

3. From apothecaries' weight to metric weight.
4. From apothecaries' weight to avoirdupois weight.
5. From avoirdupois weight to metric weight.
6. From avoirdupois weight to apothecaries' weight.
7. From metric volume to United States fluid system.
8. From United States fluid system to metric volume.

Each of these conversions will be illustrated by an example in which the calculations are explained.

1. *From Metric Weight to Apothecaries' Weight.*—What is the equivalent in the apothecaries' system for 640 Gm.?

Two factors are found in the list of fundamental equivalents that might serve for this conversion, since they are in reciprocal relationship to each other. These are 1 Gm. = 15.432 gr. and 1 gr. = 0.065 Gm. Thus grams can be converted to grains by multiplying by 15.432 or by dividing by 0.065. Wherever a choice is offered, it is usually easier to multiply than to divide. Therefore, in this case the calculation would be as follows:

$$640 \times 15.432 = 9{,}876.48 \text{ gr.}$$

It now remains to reduce this quantity to the proper denominations of the apothecaries' system. This is done by dividing the total quantity by the number of grains corresponding to the largest unit that will be contained in the total quantity. The number of grains corresponding to the next largest unit is then applied to the remainder, and the procedure continued in this fashion in descending order until the smallest unit is reached.

5,760/9,876.48/1 lb.
5,760.
480/4,116.48/8 ℥
3,840.
60/ 276.48/4 ʒ
240.
20/ 36.48/1 ℈
20.
16.48 or $16\frac{12}{25}$ gr.

Thus, 640 Gm. is equivalent to 1 lb., 8 ℥, 4 ʒ, 1 ℈, and $16\frac{12}{25}$ gr. (apoth.). It will be noted that division is made only when quantities will be contained one or more times and the process is stopped at the decimal point. This is done in order to avoid fractional parts of the larger units. It should be noted that the fractional part of the grain ($\frac{12}{25}$) is expressed as a common fraction, as is the custom for fractional parts of grains and minims. Decimal fractions are reserved for use with metric units.

2. *From Metric Weight to Avoirdupois Weight.*—What is the equivalent in the avoirdupois system for 640 Gm.? The same quantity as that used in Example 1 will also serve to illustrate conversions from metric weight to avoirdupois weight as shown below.

$$640 \times 15.432 = 9{,}876.48 \text{ gr.}$$

The reduction to proper units of the system is made as follows:

$$\begin{array}{r|l} 7{,}000 & 9{,}876.48 \;/\; 1 \text{ lb.} \\ & 7{,}000. \\ \hline 437.5 & 2{,}876.48 \;/\; 6 \text{ oz.} \\ & 2{,}625.0 \\ \hline & 251.48 = 251\tfrac{12}{25} \text{ gr.} \end{array}$$

Hence, 640 Gm. is equivalent to 1 lb., 6 oz., $251\frac{12}{25}$ g. (av.).

3. *From Apothecaries' Weight to Metric Weight.*—What is the equivalent in the metric system for 1 lb., 2 ℥, 1 ℥, 2 ℈, and 12 gr. (apoth.)?

Before conversion can be made, the total value in grains should be obtained, in order that the equivalent expressing the value of the grain in grams may be used.

1 lb.	=	5,760 gr.
2 ℥	= 2 × 480 =	960 gr.
1 ℥	=	60 gr.
2 ℈	= 2 × 20 =	40 gr.
		12 gr.
		6,832 gr. total

According to the table of fundamental equivalents, 1 gr. is equal to 0.065 Gm.

$$6{,}832 \times 0.065 = 444.080 \text{ Gm.}$$

It is customary to express quantities in metric weight in this way, rather than to list the appropriate quantities under the separate denominations of the metric system.

4. *From Apothecaries' Weight to Avoirdupois Weight.*—What is the equivalent in the avoirdupois system for 2 lb., 4 ℥, 5 ℥, 2 ℈, and 6 gr. (apoth.)?

Since the grain is the only unit common to the two systems, the total number of grains must be determined first.

2 lb.	= 2 × 5,760 =	11,520 gr.
4 ℥	= 4 × 480 =	1,920 gr.
5 ℥	= 5 × 60 =	300 gr.
2 ℈	= 2 × 20 =	40 gr.
		6 gr.
		13,786 gr. total

The total is then reduced to the proper denominations of the apothecaries' system by divisions as follows:

$$\begin{array}{r|l} 7{,}000 & 13{,}786.0 \;/\; 1 \text{ lb.} \\ & 7{,}000. \\ \hline 437.5 & 6{,}786.0 \;/\; 15 \text{ oz.} \\ & 4{,}375. \\ & 2{,}411.0 \\ & 2{,}187.5 \\ \hline & 223.5 = 223\tfrac{1}{2} \text{ gr.} \end{array}$$

Hence, 2 lb., 4 ℥, 5 ʒ, 2 ℈, and 6 gr. is equal to 1 lb., 15 oz., and 223½ gr. (av.).

5. *From Avoirdupois Weight to Metric Weight.*—What is the equivalent in the metric system for 1 lb., 2 oz., and 42 gr.? (Note that the abbreviation oz. indicates that this is avoirdupois weight.)

Again, the total number of grains must be determined first.

$$\begin{aligned} 1 \text{ lb.} &= 7{,}000 \text{ gr.} \\ 2 \text{ oz.} = 2 \times 437.5 &= 875 \text{ gr.} \\ &\quad 42 \text{ gr.} \\ &\overline{7{,}917 \text{ gr.}} \\ 7{,}917 \times 0.065 &= 514.605 \text{ Gm.} \end{aligned}$$

6. *From Avoirdupois Weight to Apothecaries' Weight.*—What is the equivalent in the apothecaries' system for 1 lb., 4 oz., and 218 gr. (av.)?

This conversion is the reverse of that shown in Example 4. First the total number of grains must be calculated.

$$\begin{aligned} 1 \text{ lb.} &= 7{,}000 \text{ gr.} \\ 4 \text{ oz.} = 4 \times 437.5 &= 1{,}750 \text{ gr.} \\ &\quad 218 \text{ gr.} \\ &\overline{8{,}968 \text{ gr.}} \end{aligned}$$

This is then reduced to the proper denominations of the apothecaries system as follows:

$$\begin{array}{r|l} 5{,}760 & 8{,}968 / 1 \text{ lb.} \\ & 5{,}760 \\ \hline 480 & 3{,}208 / 6 \text{ ℥} \\ & 2{,}880 \\ \hline 60 & 328 / 5 \text{ ʒ} \\ & 300 \\ \hline 20 & 28 / 1 \text{ ℈} \\ & 20 \\ \hline & 8 \text{ gr.} \end{array}$$

Hence, 1 lb., 4 oz., 218 gr. is equal to 1 lb., 6 ℥, 5 ʒ, 1 ℈, and 8 gr. (apoth.).

7. *From Metric Volume to U.S. Fluid System.*—What is the equivalent in the United States fluid system for 6,742 cc.?

Since 1 cc. is equivalent to 16.23 ♏, 6,742 × 16.23 = 109,422.66 ♏. It then remains to reduce this to the appropriate units of the United States fluid system.

$$\begin{array}{r|l} 61{,}440 & 109{,}422.66 / 1 \text{ gal.} \\ & 61{,}440. \\ \hline 7{,}680 & 47{,}982.66 / 6 \text{ pt.} \\ & 46{,}080. \\ \hline 480 & 1{,}902.66 / 3 \text{ f ℥} \\ & 1{,}440. \\ \hline 60 & 462.66 / 7 \text{ f ʒ} \\ & 420. \\ \hline & 42.66 \text{ or } 42\tfrac{33}{50} \text{ ♏} \end{array}$$

Hence, 6,742 cc. is equivalent to 1 gal., 6 pt., 3 f℥, 7 f℥, and $42\frac{33}{50}$ ♏.

8. *From United States Fluid System to Metric Volume.*—What will be the volume in the metric system equivalent to 1 gal., 1 pt., 6 f℥, 3 f℥, and 20 ♏?

Since the equivalent in reciprocal relationship with the equivalent of the cubic centimeter in minims was not included in the list of five fundamental equivalents previously given, the total volume, in minims, must be divided by 16.23, the number of minims in a cubic centimeter, to convert it into

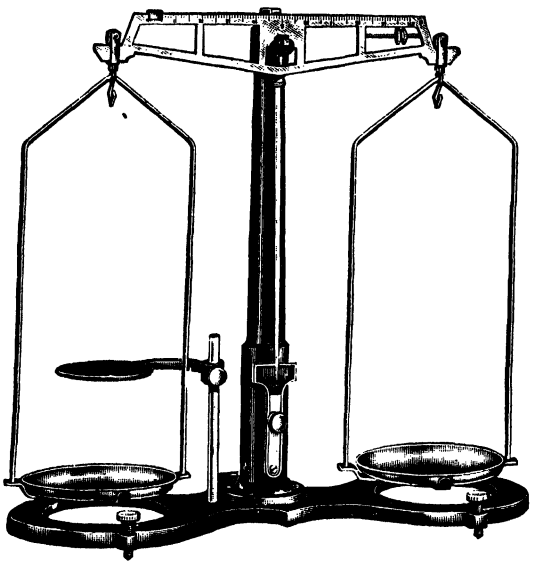


FIG. 3.—Equal-arm balance.

cubic centimeters. The calculation of the total volume, in minims, is made as follows:

1 gal. =		61,440 ♏
1 pt. =		7,680 ♏
6 f℥	= 6 × 480 =	2,880 ♏
3 f℥	= 3 × 60 =	180 ♏
		20 ♏
		72,200 ♏

$$\frac{72,200}{16.23} = 4,448.55 \text{ cc.}$$

Hence, 1 gal., 1 pt., 6 f℥, 3 f℥, and 20 ♏ is equivalent to 4,448.55 cc. This might also be expressed as 4 L. and 448.55 cc.

Weighing Instruments.—The instrument used for determining weight is usually called a balance or sometimes scales or a pair of

scales. The word *balance* is derived from the Latin word *bilanx*, which is in turn derived from *bis*, meaning "twice," and *lanx*, meaning a "plate" or "scales"; hence the word means "having two scales" or "a pair of scales." In common practice, the

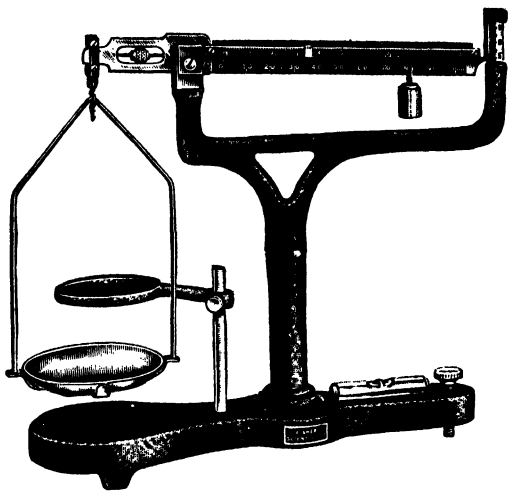


FIG. 4.—Unequal-arm balance.

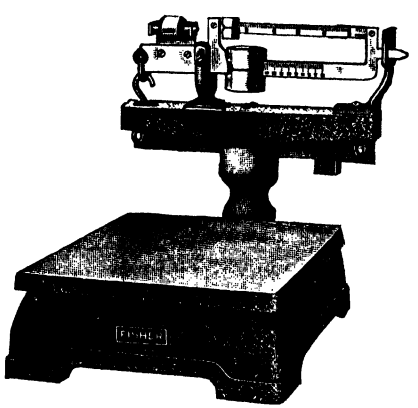


FIG. 5.—Compound-lever balance.

terms *scales* and *a pair of scales* are used in referring to instruments of limited sensitivity or those used in determining large weights, while the term *balance* is reserved for instruments capable of a higher degree of precision. The instrument used

by the pharmacist would ordinarily be sufficiently sensitive to justify the term balance rather than the term *scales* or *a pair of scales*. The earliest type of instrument used for weighing was the equal-arm balance, which applies the principle of the lever and fulcrum, one of the simpler mechanical devices discussed in all courses in physics. Other weighing instruments may depend upon the elasticity of a coiled spring (the Jolly balance or the grocer's spring balance) or of flattened steel bands under tension (the torsion balance). Only the beam type (equal arm and other modifications) and the torsion balance are used in pharmacy.

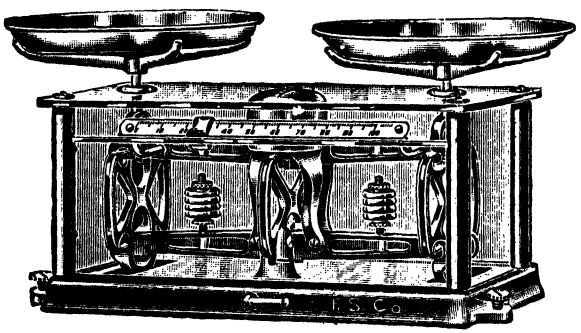


FIG. 6.—The torsion balance.

The Principle of Moments.—Regardless of the degree of refinement of the instrument or the modifications involved, all beam-type balances employ the same mechanism in one form or another, namely, that of the lever and fulcrum. According to the **principle of moments,** the force applied multiplied by the length of the arm (distance from the fulcrum to the point where the force is applied) must be equal to the product of the force acting on the opposite end of the lever and the length of the other arm.

In Fig. 7, the weight W_1 suspended from the shorter arm A_1 and having a value of 200 Gm. may be placed in equilibrium with the lighter weight W_2, having a value of 100 Gm., only if the longer arm A_2 is twice as long as the shorter arm. Mathematically, this principle may be stated as follows:

$$W_1A_1 = W_2A_2$$

and

$$200 \times 2 = 100 \times 4$$

According to this principle, it therefore is necessary in using the equal-arm balance to counterbalance the object being weighed with a counterpoise (standard weight or weights) of equal mass. In dealing with greater masses in commercial transactions upon a larger scale, advantage is taken of this principle by the use of the unequal-arm balance, or even the compound-lever balance, in which a series of levers acts one upon the other with the result that the standard weight may serve as a counterpoise for objects of many times its own weight.

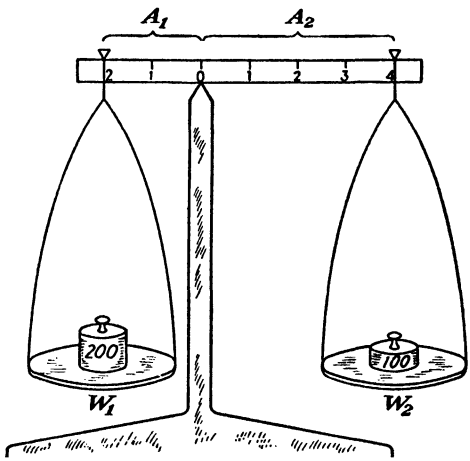


FIG. 7.—The principle of moments.

Details of Construction of the Balance.—The equal-arm balance is so constructed that the beam is supported upon a knife-edge located at the center of the beam and the pans are supported by inverted knife-edges at either end of the beam. The knife-edges may be made of specially tempered steel; or, in the case of analytical balances, they are frequently made of smoothly polished agate. In order to ensure accuracy, the beam should be as nearly inflexible as possible and constructed of light material. The bending of the beam under excessive loads tends to impair accuracy, since the effect of bending is the same as that of shortening the beam. At the same time, excessive weight of the beam assembly tends to decrease the sensitivity of the balance because of the greater inertia of the larger mass.

In practice, manufacturers attempt to effect a compromise between rigidity and lightness in weight by such devices as the use of a trusslike structure and the employment of lightweight aluminum alloys.

From the standpoint of accuracy, it is also important for the knife-edges at the ends to be equidistant from the center and for all three to be on the same plane and parallel to each other. It is also essential for the center of gravity of the beam assembly to be slightly below the point of support. The **center of gravity** of the beam assembly is that point about which it will oscillate or at which the weight is exactly compensated in every direction. If the center of gravity were above the point of support, the beam would fail to oscillate, since the center of gravity would be lowered by the swinging of the beam. The nearer the center of gravity approaches the point of support, the greater the sensitivity of the balance. Some of the better types of balance, such as those used in making analytical and other accurate weighings of small quantities, are provided with an adjustable weight on the indicator, which permits an accurate adjustment of the sensitivity of the balance by shifting the center of gravity.

Sensitivity.—The sensitivity of a balance has been mentioned in speaking of the relationship of the center of gravity to the point of support of the beam. When this term is used with reference to the analytical balance, it has special significance. Sensitivity may be defined as the number of scale divisions (on the indicator scale) by which the zero point of the balance is displaced by an excess load of 1 mg. In order to understand this definition one must know what is meant by the **zero point.** Theoretically, this is the point at which the indicator, or pointer, would ultimately come to rest if the beam were allowed to oscillate freely, protected from all outside influences, such as air currents. Actually, it is never determined in this way. Observations are made, while the beam is in motion, of the points of arrest on both the right and the left side of the scale zero, one more reading being taken on one side than the other, in order that a whole number of complete oscillations may be considered. By dividing the total of the values for each side by the number of readings on that side, the average values (average points of arrest) are obtained. The difference in the two average values,

divided by 2, gives the zero point of the balance. The position may be to the right or the left of the scale zero, depending upon which of the average values is greater.

An example of the calculation of the zero point follows. Assume that the readings for the points of arrest of the indicator that are shown below are obtained:

Left	Right
9.0	7.6
8.6	7.2
8.2	6.8
7.8	
4/33.6	3/21.6
8.4 average	7.2 average

$$8.4 - 7.2 = 1.2 \text{ difference}$$

Then $1.2/2 = 0.6$, which means that the true zero point is 0.6 of a scale division to the left of the scale zero.

Having determined the zero point of the balance with no load and no excess, the rider is adjusted in such a way as to impose an excess load of 1 mg. on the right arm of the balance, and the zero point is again determined as before. The number of scale divisions by which the zero point is displaced to the left is the measure of the sensitivity of the balance. In testing an analytical balance, it is the practice to make the test with varying conditions of load; *i.e.*, 10-, 20-, and 50-Gm. weights are placed on each pan of the balance and the sensitivity determined, in succession, under each load. As a general rule, sensitivity tends to decrease with increase in load, because of the increase in friction on the knife-edges. Refinements in manufacturing have made possible the construction of special types of balance such as those used in microanalytical weighings, which are sensitive to 1/1,000 mg. (0.000001 Gm.) at full capacity load.

Types of Balances.—The general principles involved in the construction and operation of balances were discussed briefly in the section on Weighing Instruments. The purpose of the present discussion is to familiarize the student with representative types of balance especially adapted to the needs of the pharmacist. The type of balance selected for a particular weighing depends upon the nature of the substance being weighed, the total quantity to be weighed, and the relative importance of

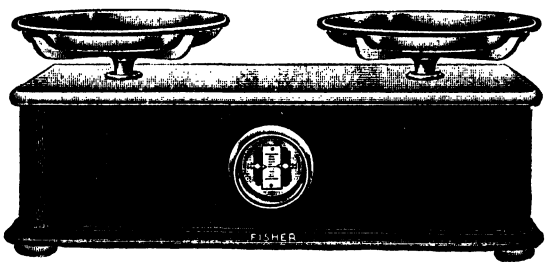
accuracy in the weighing. It is perfectly obvious that an extremely high degree of accuracy is not required in weighing a pound of magnesium sulfate that is to be sold over the counter to a customer. On the other hand, in the compounding of a prescription, particularly where potent substances such as atropine sulfate, strychnine sulfate, or morphine sulfate are required, a high degree of accuracy in weighing is vitally important. In addition, the pharmacist may, in his capacity as a pharmaceutical chemist or in the study of a research problem, require a still higher degree of accuracy in order to interpret his findings properly. For convenience, we shall speak of the three types of balance suited to the three classes of weighing just mentioned as dispensing balances, prescription balances, and analytical balances, respectively.

Dispensing Balances.—Balances of this type are used for weighing drugs and chemicals that are sold in bulk and in weighing out the solid ingredients used in manufacturing pharmaceutical preparations. In either case, balances that are of sufficient capacity to be useful in manufacturing in fairly large quantities, or to weigh relatively large amounts of material, should be available. Extremely accurate weighings are of minor importance in view of the total quantity of materials being weighed. As a matter of fact, even in preparations involving chemical reactions where two or more ingredients are required in chemically equivalent quantities, it is frequently found that the formula for these preparations as given in the Pharmacopoeia or National Formulary is carried out only to the nearest whole number of grams. A high degree of sensitivity in a balance intended for such weighings is therefore of relatively less importance than the sturdiness of its construction and its maximum capacity. Two examples of dispensing balances are shown in Fig. 8. Another balance admirably suited for such use is the large torsion balance, which is shown in Fig. 6. This balance has a capacity of 10 lb. (4.5 Kg.) and is sensitive to 0.2 Gm. (3 gr.). The mechanical principle of the torsion balance is discussed in the description of the torsion prescription balance.

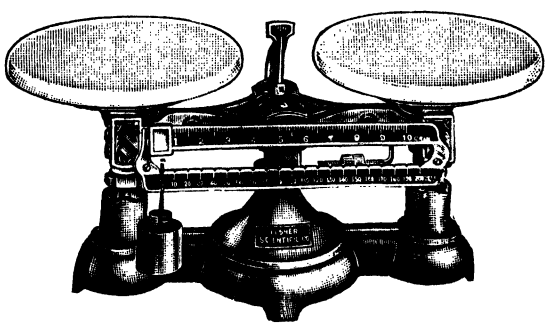
The Harvard trip balance of Fig. 8 is the form that is equipped with a double beam, each of which is provided with a sliding weight, or rider, which eliminates the need for a separate set of weights for all weighings of less than

210 Gm. The upper beam is graduated in 0.1-Gm. divisions up to 10 Gm., and the lower beam in 10-Gm. divisions up to 200 Gm. The balance is sensitive to 0.1 Gm. (1½ gr.) and has a capacity of 2 Kg. (4.4 lb.).

The marble-top dispensing balance is enclosed in a black wooden case and is available in three sizes, having maximum capacities of 7, 8, and 9 lb. (3.2, 3.6, and 4.1 Kg., respectively). The balance is equipped with two indicators, which appear at the front of the instrument, protected by a glass plate. Separate sets of weights are required with this balance.



Marble-top dispensing balance.

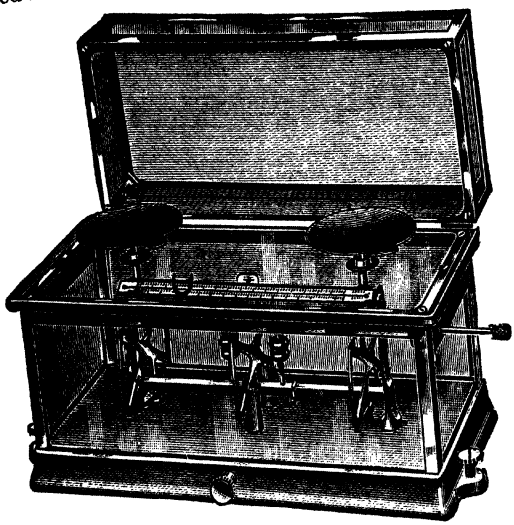


Harvard trip balance.

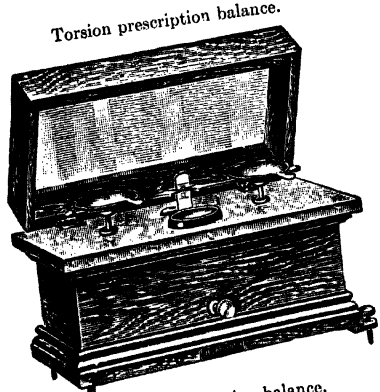
FIG. 8.—Dispensing balances.

Prescription Balances.—In the compounding of prescriptions, the sensitivity of the balance is of much greater importance than a large capacity, since a high degree of accuracy is essential and, as a rule, the total quantities to be weighed are relatively small. Balances suited for this purpose are accordingly less rugged in their construction than those designed for larger capacities, greater attention being given to refinements that contribute to the sensitivity of the balance. Two examples of prescription balances are shown in Fig. 9.

The entire beam assembly of the enclosed prescription balance is contained in a wooden case with a hinged cover provided with



Torsion prescription balance.



Enclosed prescription balance.

FIG. 9.—Prescription balances.

a glass top. The pan arrest is controlled by the knurled knob, which is located at the front of the case. Two indicators are provided on this instrument, which requires a different method

for determining when the balance is in equilibrium from that used for the balance provided with a single indicator. Since each indicator is geared to the corresponding end of the beam, it must follow that each will move a like distance in opposite directions from the scale zero. Hence, the distance of travel from the scale zero for each indicator is always equal to that of the other, whether the balance is in equilibrium or not. When the balance is in equilibrium, the weights must be so adjusted that the two indicators show approximately the same maximum separation for two swings in succession. Or it may be said that equilibrium is established when the rise above the zero point for one of the indicators, on the upward swing, is approximately equal to the fall below the zero point of the same indicator on the downward swing. The balance illustrated has a capacity of 1 ℥ (30 Gm.) and is sensitive to ¼ gr. (0.015 Gm).

Probably the most satisfactory balance for prescription room use is the **torsion prescription balance.** The greater sensitivity of this balance fully justifies its greater cost when compared with ordinary prescription balances using rigid beams supported by knife-edges. The loss of sensitivity due to increased friction upon the knife-edges with an increase in load, which is characteristic of these balances, is almost completely eliminated in the torsion balance.

The operation of the torsion balance is based upon the elasticity, or resiliency, of tempered steel bands under tension when subjected to twisting or torsion. Some idea of the details of construction may be gained from Fig. 10. It will be noted that the beam assembly consists of two parallel beams attached to each other by three steel bands. The bands are tightly stretched over trusslike frames, which are X-shaped in design. The frames at the ends serve to support the balance pans, while the weight of the beam assembly rests on the center frame. The points of attachment are indicated at A and A' for the center frame and at B and B' for the end frames. At these points, the flat band is firmly clamped in position, so that any tilting of the beam assembly results in a twisting, or torsional, effect, which is applied simultaneously at the six points of attachment of the steel bands.

As the beam oscillates, the frame members remain in a vertical position, parallel to each other. However, the slightest movement of the beam from its horizontal position, in either direction, distorts the rectangle outlined by the upper and lower beam and the two end frames to form a parallelogram. The greater the distortion, the greater the forces set up by the steel bands in tending to overcome this distortion. Thus it can be seen that the tendency

of torsional resistance is to maintain the beam in a horizontal position. Since the forces that are set up are considerable, the problem of partly overcoming these forces, or reducing them, had to be solved before the balance could be made to respond to slight differences in load.

The ordinary beam-type balance will not function if the center of gravity of the beam assembly is above the point of support, since the swinging of the beam to either side lowers the center of gravity and the beam remains in that position. In the torsion balance, the reverse is true. The center of gravity is purposely placed above the point of support so that the force of gravity may be used to compensate for the torsional forces which are set up as the beam oscillates. In order to bring this about, counterbalancing weights (not shown in the figure) are attached to the upper side of the lower beam. The sensitivity of the balance depends upon the delicate adjustment of these weights, both as to size and position, so as almost completely to

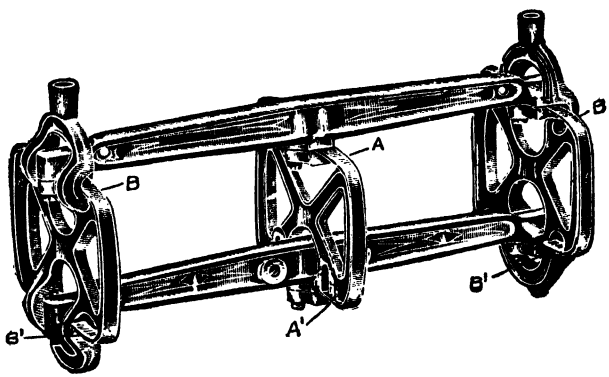


FIG. 10.—Construction of the torsion balance.

offset the torsional forces of the steel bands. The nearness of the approach to equilibrium between the effect of gravity, as determined by the location of the center of gravity, and the torsional effect, which depends upon the degree of tension upon the steel bands and the kind of steel used in their manufacture, determines the sensitivity of the balance.

The balance is enclosed in a glass case, with a plate-glass top and a hinged glass cover. Its beam is provided with a rider, which is operated by a rod extending from the right end of the case. Two scales for the rider are shown on the beam, one graduated in grains and extending from 0 to 15 gr., in $\frac{1}{8}$-gr. divisions, and the other in grams, extending from 0 to 1 Gm., and subdivided into 0.10-Gm. divisions. The same rider serves for both scales and greatly facilitates the weighing of small quantities by eliminating the necessity for handling small weights. The beam is provided with double indicators, which move up and down over a fixed scale. A beam arrest is provided, which is operated by turning a knurled knob located at the front of the case. This takes the weight of the beam assembly off the steel bands

and should be kept locked in position at all times when the balance is not in use. The torsion prescription balance has a capacity of 4 ℥ (120 Gm.) and is sensitive to 1/32 gr. (0.002 Gm.).

Analytical Balances.—The balances used for analytical weighings are precision instruments capable of a degree of accuracy which probably surpasses that of most other instruments used in making physical measurements. The balances shown and described here represent types widely used in analytical laboratories. Fundamentally, all these are similar in construction, differing principally with respect to the accessories and refinements that have been added or in the way in which the final adjustment of weight is made, as in the use of a gold chain to replace the conventional rider.

Becker Analytical Balance.—The model shown in Fig. 11 is a typical example of the rider type of analytical balance. All analytical balances are equipped with a mechanism known as a pan arrest, which serves to prevent excessive swaying of the pans and to support the beam assembly while making minor adjustments in weight. This device is operated independently of the beam-arrest mechanism, which is controlled by the larger milled knob shown at the front of the case. The control for the pan arrest is located immediately to the left. Because of the delicacy of analytical weighings, a balance designed for such use is always provided with a glass case in order to afford protection from air currents, which would otherwise interfere with the accuracy of the weighing. The door of the case is always closed before making the final adjustment of weights necessary to complete the weighing. In order to operate properly, the balance must be perfectly level, and, for convenience in making this adjustment, a spirit level is usually provided. In older types of balance, a plumb line was used. The balance rests on three points of support, two of which are located at the front of the balance case, the third being centrally located at the rear. The front legs are adjustable in height. The object to be weighed must be counterbalanced by an equal quantity of standard or calibrated weights, which are transferred to the right-hand balance pan in sufficient quantity to come within 10 mg. of the final total. At this point the balance case is closed, and the final adjustment is then made with the rider, a small platinum wire that straddles the beam and that may be moved to any desired position with the rider rod, which is manipulated from outside the case. The rider has a weight of 10 mg. when placed at the extreme end of the beam, but its effect decreases proportionately, in accordance with the principle of moments, as it is moved nearer the fulcrum or central knife-edge. The scale on the beam gives its value for any position it may occupy.

Before a balance may be used for weighing, it must be inspected to make certain that it is level and then checked for equilibrium by determining the

position of the zero point at no load and no excess weight. In most cases, it is desirable that the actual zero, or null point, be made to coincide with the scale zero. If this is found not to be the case, adjustment is made by changing slightly the position of one of the adjusting screws, shown at either end of the beam. Even after this has been done, it is frequently found that, after a few hours have elapsed, possibly because of the collection of dust particles on the moving parts of the beam assembly the zero point may have

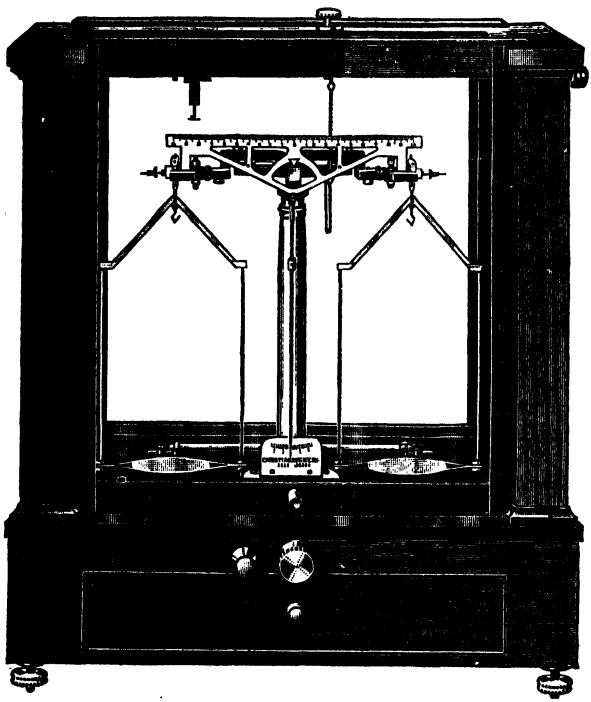


FIG. 11.—Becker analytical balance.

shifted slightly. To correct for such minor deviations, the balance shown is equipped with a patented device known as the equilibrium adjuster, which consists of a looped gold chain, one end of which is attached to the beam at a point to the right of the fulcrum, while the other end passes through the top of the case. By turning a thumbscrew, the weight of the chain supported by the beam may be varied sufficiently to restore equilibrium. This device has the advantage of permitting adjustments to be made from outside the case while the beam is in motion. According to the manufacturer, this balance is sensitive to 0.05 mg. and has a total capacity of 200 Gm. on each pan.

Ainsworth Keyboard Analytical Balance.—An operation in analytical weighings that is tedious and time-consuming is the placing of the weights

on the balance pan, each weight being handled with forceps. Since the trial-and-error method is used, this means that several weights may be placed on the pan which have to be removed, because the total weight exceeds that of the object being weighed. The Ainsworth keyboard analytical balance, shown in Fig. 12, represents a modern improvement in analytical balances that is designed to eliminate the necessity for handling the

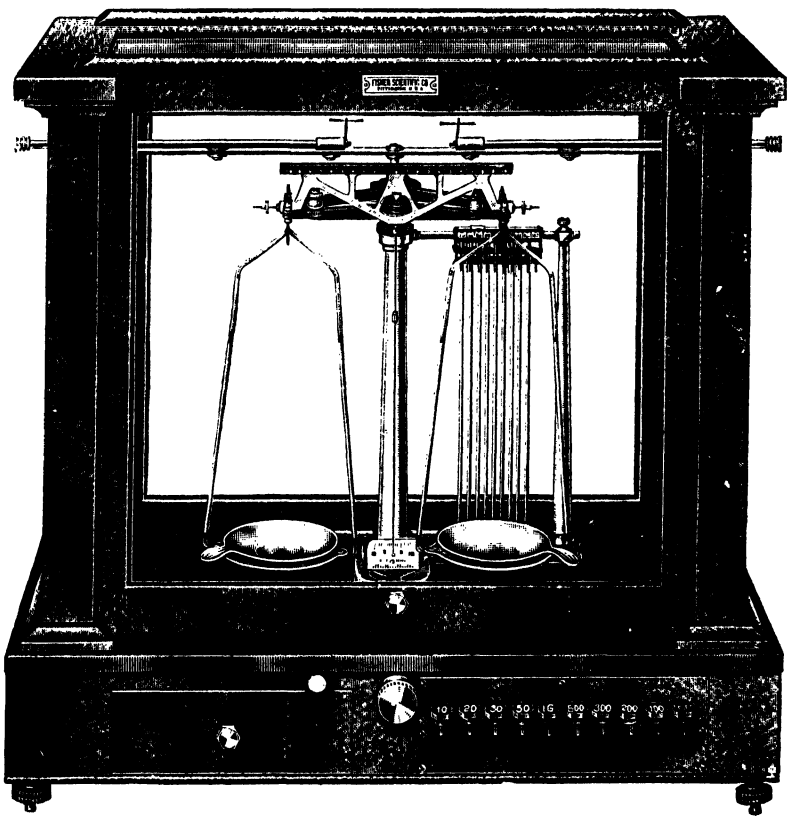


FIG. 12.—Ainsworth keyboard analytical balance.

smaller weights. By means of an ingenious keyboard arrangement, each of the smaller weights, ranging from 1 Gm. downward, may be transferred directly to the beam by simply pressing the appropriate key located at the front of the balance case. A return key automatically clears the beam of all weights at a single operation. A check of the depressed keys serves to indicate which of the weights are in position on the beam at any time. The total weight accounted for by the automatic keyboard is 2.210 Gm., subdivided into separate weights having the following values: 1 Gm.; 500, 300,

200, 100, 50, 30, 20, and 10 mg. The principal advantage of this type of balance lies in the saving in time which can be made in the selection and transfer of weights. This balance has a capacity of 200 Gm. on each pan and, according to the manufacturer, is sensitive to 0.025 mg. at full load.

Ainsworth Chainweight Analytical Balance.—Another method of avoiding handling the smaller weights, and at the same time permitting slight increases

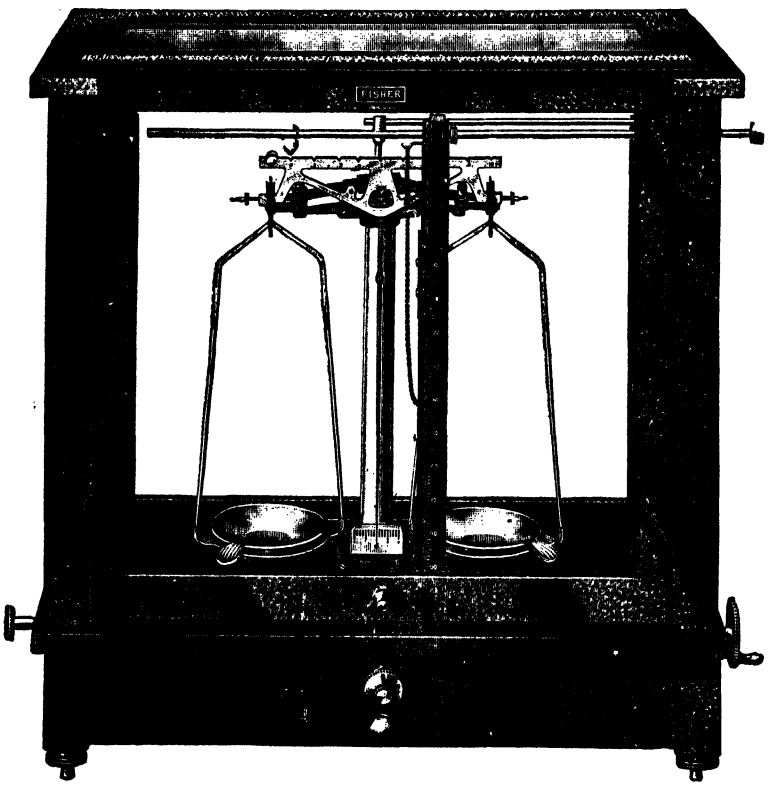


FIG. 13.—Ainsworth chainweight analytical balance.

or decreases in weight to be made while the beam is in motion, involves the use of a gold chain, which usually covers a range of 100 mg., as a substitute for the smaller weights. Two manufacturers have developed balances equipped with devices of this kind. One of these, the Ainsworth chainweight analytical balance, is shown in Fig. 13.

The chain is arranged so that one end is attached directly to the beam at a fixed distance to the right of the fulcrum while the other end is attached to a movable support operated by a rack-and-pinion device or by means of a flexible steel tape. Theoretically, the weight of that portion of the chain

pendent from the beam is constant only at one point, which is when the beam is in a horizontal position, or at rest. Tilting the beam in either direction changes the loading on the beam. However, in the case of a balance of high sensitivity, this is an advantage rather than a disadvantage, since under normal conditions the beam shows rather wide oscillations for minute differences in weight, and the action of the chain serves to exert a retarding influence upon the amplitude of the oscillations. This effect resembles, without exactly duplicating, the effect of magnetic damping to be described later in this chapter.

The style of balance illustrated in Fig. 13 is the Ainsworth chainweight analytical balance equipped with the notched beam and the 1-Gm. rider-type weight. This combination mechanizes the transfer of all weights of less than 1 Gm. The chainweight device is actuated by a flat steel spring, which is controlled by the knob shown at the right side of the balance case. The tape is graduated throughout a 100-mg. range and is read by comparison with a fixed vernier. This offers the advantage of permitting all readings to be made at the normal eye level. The vernier has a slight movement, which is controlled by the knob shown at the left side of the balance. This permits adjustment of the zero point to correspond with the zero of the scale by raising or lowering the chain, as may be required. The vernier may then be adjusted so that its zero coincides with the zero of the steel tape. This permits the balance to be brought to equilibrium without the necessity for adjusting the counterpoises located at the ends of the beam. The adjustable vernier on this balance serves the same purpose as the Auto-Dex, or adjustable scale of the Becker chainomatic balance to be discussed in the next section. The capacity of the Ainsworth chainweight balance is 200 Gm., and it is sensitive to 0.05 mg.

Becker Chainomatic Analytical Balance.—The essential difference in this balance, which is shown in Fig. 14, and the balance just described lies in the mechanism used to shift the position of the chain and the fact that a movable vernier is used instead of the fixed vernier. One end of the chain is attached to the vernier, which may be raised or lowered by rotating the knob shown at the right of the balance. The beam of this balance is also of the notched type and is equipped with a 1-Gm. rider-type weight, which eliminates the need for handling any weights of less than 1 Gm. The index scale of the instrument is geared to a mechanism known as the Auto-Dex, which may be operated by the knob shown at the extreme left of the front of the balance. This arrangement permits shifting of the position of the scale to the right or left in order to compensate for minor deviations in the equilibrium of the balance. The balance is also equipped with the equilibrium adjuster described under Becker Analytical Balance. The capacity of the balance is 200 Gm. on each pan, and it is sensitive to 0.05 mg. under full load.

Ainsworth Microanalytical Balance.—One of the fields of analytical chemistry that have seen a considerable development in recent years is microanalysis. In special types of research work involving difficult procedures of synthesis or in the isolation of compounds from naturally occurring sources where the yields are exceedingly small, it is sometimes extremely

difficult to obtain appreciable quantities of the pure substance for analysis. Under the influence of Pregl, Emich, and others, new methods of analysis have been developed to meet such conditions.

In order to meet the exacting conditions of microanalysis, special balances must be used that extend the limit of accuracy far beyond that of the ordinary analytical balance. With ordinary methods of procedure, we are accustomed to think in terms of **milligrams**, while the microchemist thinks in terms of **gammas**. (A **gamma**, also known as a **microgram**, is equivalent to 0.001 mg.) As an example of a balance suitable for this type of analysis,

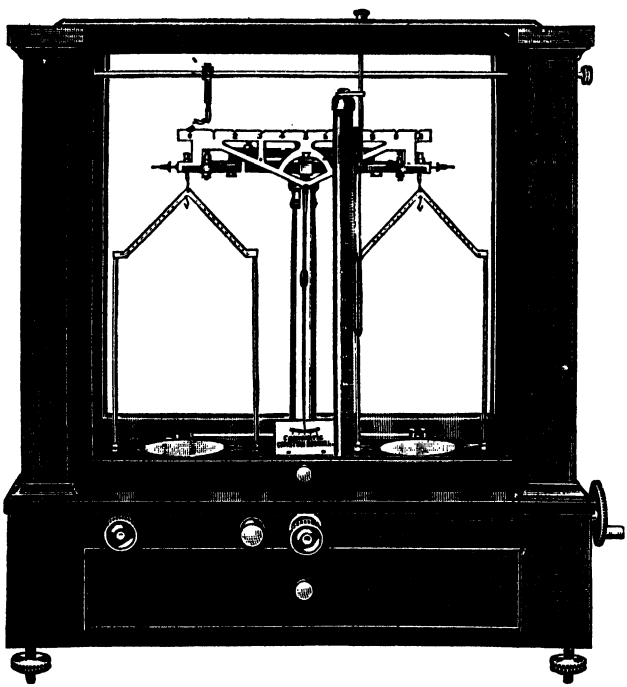


FIG. 14.—Becker chainomatic balance.

the Ainsworth microanalytical balance is shown in Fig. 15. Since relatively small weighings are involved, the capacity of the balance is limited to 20 Gm. Provision is made for two riders on the beam, of 5 and 0.5 mg. each. The beam is graduated from left to right in 100 spaces, and there are 201 notches on the beam. Accordingly, the larger rider may be set to the nearest 50 gammas and the smaller rider to the nearest 5 gammas. The balance is equipped with magnifying lenses for reading the indicator index and the position of the rider. According to the manufacturer, since 10 divisions are equivalent to 0.1 mg., it is possible to estimate in terms of gammas.

Magnetic Damping Device.—A close relationship exists between the sensitivity of a balance and the rate at which the beam oscillates. In general, the greater the sensitivity, the slower the rate of swing. Since this characteristic is inherent in the analytical balance, it follows that accurate weighings with a balance of this type require considerable time because of the slow rate of oscillation of the beam. An appliance that utilizes the principle of magnetic attraction to decelerate the movement of the beam and bring

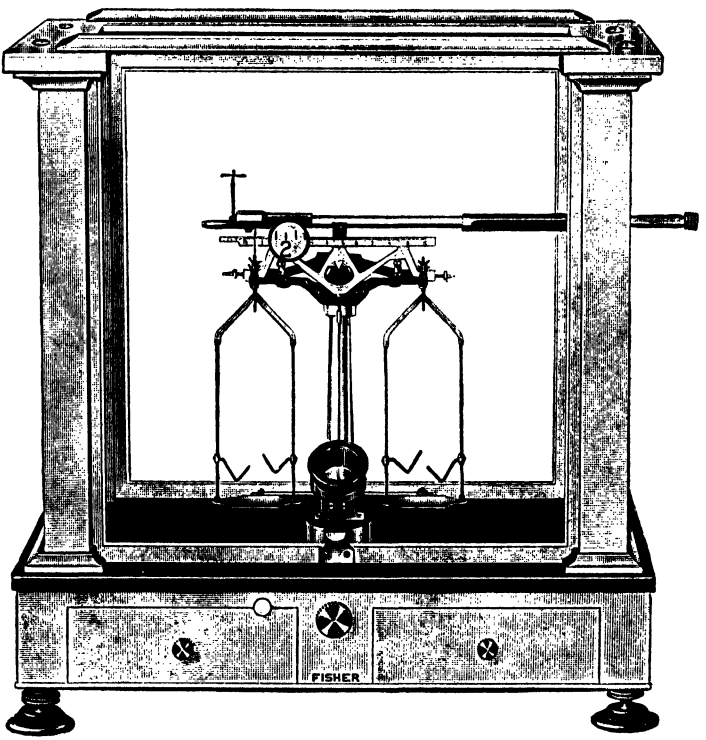


FIG. 15.—The Ainsworth microanalytical balance.

it to a standstill is represented by the magnetic damping device that is shown in Fig. 16.

The apparatus consists of an aluminum plate with a weight, which serves to counterbalance it, and a permanent horseshoe magnet, supplied with an arm for attaching it to the pillar of the balance. As the plate moves up and down between the poles of the magnet with the movement of the beam, eddy currents are set up in the plate, which, by magnetic attraction, retard the movements of the beam and bring it to a halt at its true rest point within 15 to 20 sec. It should be understood that this attraction exists only while the plate is in motion; once the movement of the beam has been arrested,

the beam is freely suspended. This device does not interfere in any way with the accuracy of the weighings and is particularly useful in conserving time in analytical laboratories where large numbers of weighings are required.

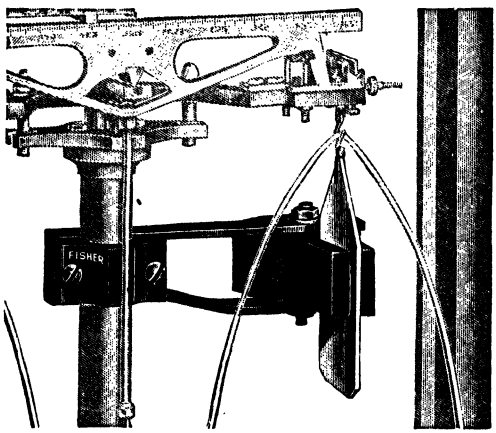


FIG. 16.—Magnetic damping device.

Weights.—Just as the selection of the type of balance depends upon the nature of the substance to be weighed, the total quantity to be weighed, and the relative importance of accuracy in the weighing, the same factors have a bearing upon the selection of weights. Wide differences may exist in the quality of weights and in the accuracy with which they are adjusted and calibrated. In general, the quality and degree of precision of the weights should correspond to the sensitivity of the balance with which they are to be used. It is apparent that ordinary commercial weights, suitable for approximate weighings, would be inappropriate for use with the analytical balance. Because of the inaccuracies of the weights, the purpose of the sensitive analytical balance would be defeated. Similarly, the use of carefully calibrated analytical weights for weighings carried out on a balance intended for approximate weighings, such as the dispensing balances described in this chapter, would be equally unjustifiable.

All weights used in the United States must agree within certain tolerances with the international kilogram, which is represented by the platinum-iridium cylinder held at the **International Bureau of Standards,** near Paris, France. The United States

has two authentic replicas of this original standard, which are held by the **National Bureau of Standards** in Washington, D.C., and used as the primary standards against which all the working standards of the bureau are checked. Certain types of precision weight are accepted by the bureau for checking, in accordance with the regulations contained in "*Design and Test of Standards of Mass,*" *National Bureau of Standards Circular* 3. This information is supplemented by various *Letter Circulars* issued from time to time by the bureau and giving the schedule of fees for the various tests and a description of the types of certificate issued by the bureau.

Space does not permit a complete listing of the specifications, tolerances, and descriptions of all the classes of weights defined by the National Bureau of Standards. For detailed information on these, the publications of the bureau previously cited, together with *National Bureau of Standards, Scientific Paper* 527, should be consulted. A few of the classes of weights will be briefly mentioned for the purpose of indicating the special uses for which the weights of each class are intended. Class M weights are for use as primary laboratory reference standards against which other weights may be checked, or in work where the highest precision is necessary. These weights must be of one-piece construction and made of hard, nonporous, nonmagnetic metals resistant to corrosion. If made of brass, bronze, or other materials that tarnish upon exposure to air, they must be plated with gold, platinum, or other suitable tarnish-proof metal. The fractional pieces should be made of platinum, although the use of aluminum for the pieces from the 20-mg. weight on down is permitted.

Class S weights are intended for use in most of the accurate weighings of scientific laboratories. Screw-knob weights are permitted in this class, and the larger pieces, down to the 1-Gm. weight, may be made of bronze or brass. Unless the material is, at least, as resistant to corrosion as nickel, it must be plated with gold, platinum, or nickel or must be lacquered. The fractional pieces down to the 50-mg. piece must be made of platinum, and the smaller pieces may be made of aluminum. Weights of this class must be adjusted to the same tolerances as those required for Class M weights.

Class S-2 weights are intended for use in routine laboratory weighings and include the usual student grade of analytical weights. They are required to conform to the specifications of design and materials required for Class S, except that the fractional pieces may all be made of aluminum or other suitable material of low density. The permitted tolerances for weights of this class are five times those permitted for Class S weights.

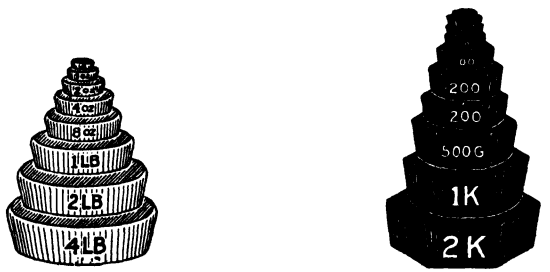
Class C consists of commercial test weights intended for use in work where a superior quality of weights is required for commercial or industrial purposes. The weights of this class, being intended for technical purposes, are permitted to have considerably wider tolerances than the classes previously described, varying for different sizes of weights. In general, the ratios of tolerances average ten to fifteen times the corresponding values for Class S-2.

Class T represents another technical class known as trade weights. The tolerances for these weights are still wider than those for Class C, approximating ten times the values for some of the smaller weights and fifteen times these values for others. Some idea of the actual values of these tolerances may be gained by noting the permitted deviation for the three sizes of weights, which are listed here, immediately followed by the tolerance for that size of weight: 1 Gm., 20 mg.; 100 Gm., 300 mg.; 1 Kg., 1 Gm.

Dispensing Weights.—Weights for ordinary commercial weighings are frequently made of cast iron or, less commonly, of brass. Since commercial transactions involve the use of the avoirdupois system and since more frequently in manufacturing pharmaceutical preparations the metric system is used, weights representing both systems should be available. Typical sets of each of these are shown in Fig. 17. Both sets are made of cast iron, galvanized and aluminum painted to prevent rusting. The avoirdupois weights are circular in outline and so designed that they may be stacked one upon the other in the order of decreasing size. The weights in the set shown range from ¼ oz. up to 4 lb. The metric weights are similar but are hexagonal in shape in order to prevent confusion with the avoirdupois weights. The weights of this set vary in size from 5 Gm. to 2 Kg.

Prescription Weights.—Two kinds of weights are required for prescription compounding, apothecaries' system and metric

weight. The quality of weights for this use should be that of Class S-2. One variety of apothecaries' weights consists of the coin type for units down to the half scruple, the smaller units being made of rectangular pieces of sheet aluminum or of aluminum wire. It should be noted that the coin type of weights,



Avoirdupois weights. Metric weights.

FIG. 17.—Commercial weights.

which are usually made of brass, shows large characters indicating the denominations in relief upon the surfaces. This roughness constitutes a source of error since such weights are likely to accumulate dirt and dust particles. Because of this tendency, the use of coin-type weights is prohibited in some states. The cylindrical form of weights, with smooth surfaces, similar in

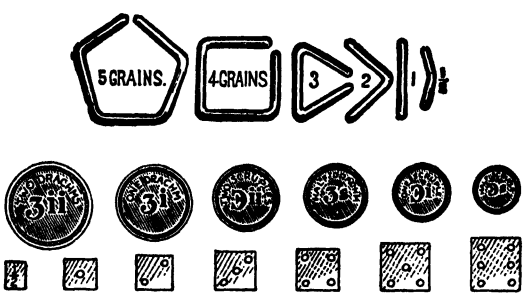


FIG. 18.—Apothecaries' weights.

appearance to metric weights, is to be preferred. Typical sets of apothecaries' weights are shown in Fig. 18.

Typical sets of metric weights suitable for prescription use are shown in Fig. 19. It should be pointed out that, if the torsion prescription balance is used, all need for fractional weights of

the metric system and for grain weights for units less than the half scruple is eliminated, since the rider of the balance will serve for weighings up to 1 Gm. (15 gr.).

Analytical Weights.—Weights used for analytical weighings should be of Class S-2 or, preferably, of Class S. It should be understood, however, that, even though the set of weights does

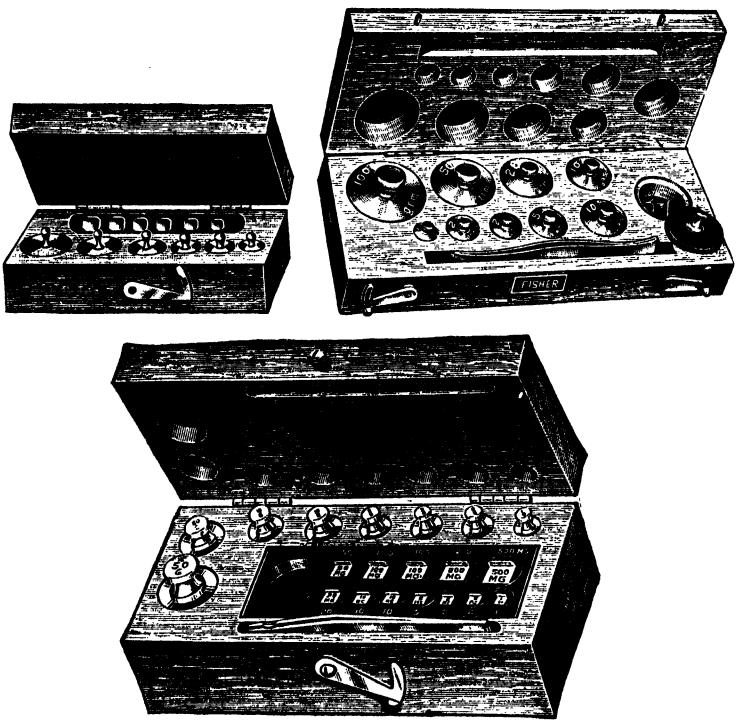


FIG. 19.—Metric prescription weights.

not conform to the specifications for either of these classes, they may be used with equal accuracy if the weights are previously calibrated by comparison with standard weights of known value and the exact value of each weight is carefully ascertained. This requires the use of correction factors for each weight that deviates from the standard value. A typical set of analytical weights (which are always in the metric system) is shown in Fig. 20. All sets of analytical weights are supplied with a pair of forceps for handling. These should have tips of plastic, ivory, or similar

material, since forceps with metallic tips are likely to mar the surface of the weights and ultimately cause a loss in weight due to wearing away of the metal.

Weights should be kept clean and bright at all times and may be refurbished by rubbing with a soft cloth dipped in jewelers' rouge or a mixture of precipitated calcium carbonate and glycerin.

FIG. 20.—Analytical weights.

Care and Use of the Balance.—Although a number of suggestions concerning the use of the balance are found in the preceding discussion of the various types of balance, a few basic principles and rules of procedure should be thoroughly understood before attempting a weighing. With the possible exception of the balances discussed under Dispensing Balances, it must be appreciated that the balance is an expensive instrument, capable of a high degree of accuracy, and that as a consequence of its high sensitivity it must be regarded as a delicate instrument which must be used properly in order to maintain its accuracy. Careless handling or the improper procedure in weighing may result in serious damage to the delicate knife-edges, which may completely destroy the accuracy of the instrument.

As a matter of general procedure, and with special reference to prescription and analytical balances, the choice of location of

the balance in the laboratory is important. Insofar as possible, the balance should be placed on a firm support where it will be protected from vibration. This may be accomplished by installing it on a bench or table located immediately above a structural support, such as a supporting wall or girder that rests on the foundation of the building, or by placing it on a shelf that is anchored in an outside wall of the building.

The room in which the balance is installed should be kept as free as possible from acid fumes and other corrosive vapors, since these are one of the most serious sources of damage. When it is necessary for the balance to be installed in the same room where the mineral acids, ammonia water, formaldehyde solution, and other volatile substances producing corrosive vapors are stored, the plan of installing the balance in a special balance case, made of glass with sash doors, is strongly recommended. The doors to the case should be kept closed at all times when the balance is not in use.

With the exception of balances equipped with magnetic damping, the determination of equilibrium is always made while the beam of the balance is in motion. For the balance with a single indicator, assuming that the zero point of the balance coincides with the scale zero, this is usually determined by so adjusting the weights that the swing of the indicator on one side of the zero of the scale is equal to the succeeding swing on the opposite side. For balances equipped with double indicators, a slightly different technique is required, which was explained in the section on Dispensing Balances.

The object to be weighed is always placed on the left-hand pan of the balance, and the counterbalancing weights are placed on the right-hand pan. This procedure is required for all balances having a rider scale extending from left to right over the full length of the beam. If the positions are reversed, it is impossible to use the rider for making the final adjustment of weights. Even if the rider scale is divided into two halves, with the zero mark at the center of the beam, the custom of placing the weights on the right-hand pan is usually followed.

In order to avoid errors in addition of the weights used, the so-called "triple-check" method is recommended. As the weights are taken from the case and placed on the balance, their

total weight is computed, in the decreasing order of size. Then the vacant spaces in the weight case are noted, and the sum of the missing weights is used as a check on this total. Finally, the total weight is again computed as the weights are removed from the balance pan and returned to the case.

Another rule that should be strictly observed is never to place a chemical substance directly in contact with the metallic surface of the balance pan. For larger balances, the use of powder papers is recommended. For prescription and analytical balances, the use of counterbalanced watch glasses of the same diameter as the balance pans will be found convenient. The reasons for this rule should be obvious. Many chemical substances will react chemically with the metal of the balance pan, producing a tarnished appearance and roughening the surface. In time, a sufficient change in the weight of the pan may be produced to exceed the limits for which adjustment may be made by means of the compensating adjusting screws located at the ends of the beam. For similar reasons, volatile corrosive liquids, such as nitric acid or hydrochloric acid, should never be weighed on a balance, unless enclosed in a weighing bottle equipped with a ground-glass stopper in order to prevent escape of the vapors. The balance pans should always be kept clean and polished. They may be burnished in the same manner as described under Weights (page 171).

In the use of the prescription balance and the rider-type analytical balance, no changes of weights or alteration of the amount of material on the left-hand pan is ever made without locking the beam firmly at rest, by the use of the beam arrest, the pan arrest, or both. This is to protect the delicate knife-edges and the agate bearings from the effect of shock that would otherwise result. The only weight that may be applied to the beam of the analytical balance while it is in motion is the rider, or a slight shifting of the chain is permitted on the chainomatic or chainweight balance under the same conditions.

Another rule to be carefully followed is for hot objects always to be permitted to cool to room temperature before being placed on the balance pan. The observance of this rule is necessary if accurate weighings are to be obtained. The heat radiated from the object interferes with the accuracy by setting up air currents

in the balance case and also causes unequal expansion of the beam, which is another source of error.

The door of the balance case must be closed before making the final adjustment of weights in order to give protection from air currents.

All weights are to be handled by means of forceps and should never be touched with the fingers. Heavy weights should be placed near the center of the pan to decrease swaying.

Testing the Balance.—Before attempting a weighing on the analytical balance, the following inspections and tests should be made in order to ensure that it is properly adjusted for accuracy: (1) Make certain that the balance is level, as indicated by the spirit level. (2) Test the operation of the beam arrest to see that it works smoothly and freely. (3) Check the adjustment of the pan-arrest mechanism to make certain that contact is made with both pans when the beam assembly is lowered and that, when locked, the mechanism does not interfere with the free oscillation of the balance pans. (4) Make certain that the indicator stands at zero when the beam is arrested, by means either of the beam arrest or of the pan arrest. (5) Check the zero point of the balance (as explained under Sensitivity) to see that it coincides with the scale zero of the balance. If all these conditions are fulfilled, it may be assumed that the balance is properly adjusted for weighing.

Cleaning the Balance.—In order to function properly, the analytical balance must be kept clean at all times, particular attention being given to the bearing surfaces of the knife-edges and the moving parts, including the beam-arrest and the pan-arrest mechanisms. The directions that follow outline the proper procedure to be followed in the routine care of the balance:

First remove the hangers and stirrups, by grasping the indicator just below the beam, lifting the beam slightly, and at the same time releasing the beam-arrest mechanism. It will be found that the stirrups may be lifted from the supporting yokes, first from one end, and then from the other. The beam may then be removed from the center bearing, care being taken not to strike the edges of the agate bearing, or to bend the end of the indicator. Brush the beam with a soft camel's-hair brush to remove dust particles.

The agate knife-edges and bearing surfaces should be cleaned with soft tissue paper moistened with alcohol or gasoline. Cloth should not be used because it may deposit lint. Care should be taken not to touch the beam or other lacquered surfaces with alcohol, for this will remove the lacquer.

Brush out the grooved supports that carry the agate knife-edges of the stirrups with a stiff toothbrush. Dirt collected in these grooves tends to cause the stirrups to stick and to release unevenly.

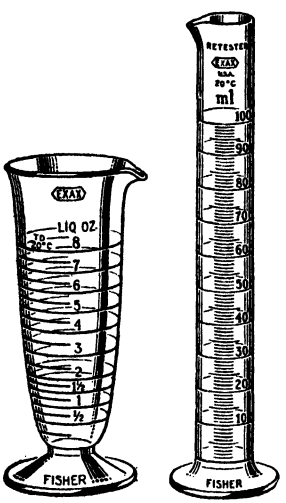
Wipe the glass surfaces of the base and the case with chamois skin; wool or silk cloth should not be used, for they will produce static electricity. Using the least possible quantity of a high-grade light oil, lubricate the metal bearings and the sliding-contact surfaces of the pan-arrest and of the beam-arrest mechanism. Care should be taken not to use excessive quantities of oil, as this tends to collect dust and causes the mechanism to become sticky. **No oil should be placed upon the agate bearings.**

The balance may now be reassembled, the beam first being replaced, and then the stirrups at either end of the beam. Make certain that the beam is in proper alignment with the contact surfaces of the arresting mechanism and that the stirrups are fitted properly into the grooves of the supporting yokes. The only additional adjustment which may be required will be that of the adjusting screws at either end of the beam to restore equilibrium to the balance.

Instruments for Measuring Volume.—According to the twelfth revision of the Pharmacopoeia, in the discussion of Volumetric Apparatus, page 744, the units of volume are required to be in accordance with the standard liter of the Pharmacopoeia at 25°C., which represents the volume occupied by 996.04 Gm. of distilled water, weighed in air, with brass weights, at 25°C. The National Bureau of Standards has adopted the true liter, which is the volume of 1 Kg. of distilled water at 4°C., except that the weight is adjusted to conform to the corresponding volume at 20°C. In view of this fact, the Pharmacopoeia states that volumetric apparatus calibrated at temperatures other than 25°C. may be used, provided that the volumetric solutions are standardized at the same temperature or that suitable temperature corrections are made. As a matter of fact, practically all volumetric apparatus is calibrated at 20°C. in conformity with the requirements of the Bureau of Standards. A brief summary of the specifications for volumetric flasks, cylinders, transfer pipettes, and burettes is found in the section on Volumetric Apparatus previously cited in the Pharmacopoeia, which should be consulted for details.

Graduates.—A commonly used measuring device for dispensing liquids is known as the graduate, which consists of a conical or cylindrical container accurately subdivided into units of volume of the metric or United States fluid system, or both. Examples

are shown in Fig. 21. The cylindrical graduates are usually subdivided in the units of the metric system only, while conical graduates may be obtained with subdivisions in either the United States fluid system or the metric system, or both. The latter form is to be preferred since both systems are widely used in pharmacy. Cylindrical graduates are available in 5-, 10-, 25-, 50-, 100-, 250-, 500-, 1,000-, and 2,000-cc. sizes. Conical graduates with the dual scale may be obtained with capacities of 1, 2, 4, 8, 16, and 32 f℥, corresponding approximately to 30, 60, 125, 250, 500, and 1,000 cc., respectively. Still smaller graduates of this type, graduated in the U.S. fluid system, of 1 and 2 f℥ capacity, the so-called "minim" graduates, are also available. Conical graduates having the graduation marks molded into the glass walls are sometimes used for measurements in technical processes, such as the preparation of developing solutions and fixing baths used in photography; but these have been found unsuitable for pharmaceutical use because of their lack of accuracy. Graduates approved by the Bureau of Standards must be individually calibrated, the graduations being etched upon the walls of the graduate. In general, the size of the graduate to be used for a given measurement should be chosen with reference to the volume of liquid to be measured. In all cases where the total volume to be measured is less than one-tenth the total capacity of the graduate, a smaller graduate is recommended.



Conical. Cylindrical.
FIG. 21.—Graduates.

A characteristic behavior of aqueous liquids and all others that have the ability to wet a glass surface is the formation of a concave surface, or meniscus. This is discussed in greater detail in Chap. VIII under the section on Capillarity. Although this effect is less apparent in graduates, it is especially pronounced in narrow containers such as burettes and pipettes. As indicated in Chap. VIII, the proper procedure is to read the lowest point of

the meniscus, which is held at the level of the eye. This applies to all except deeply colored liquids having menisci that are difficult to read; these should be read at the top of the column of liquid. Cylindrical graduates, measuring and transfer pipettes, and burettes approved by the Bureau of Standards are required to show graduations at stated intervals that completely encircle the instrument. This arrangement is useful as a guide in determining when the meniscus is at eye level, since, under these conditions, the graduation will appear as a straight line, rather than as an ellipse.

Volumetric Flasks.—Although the principal use of volumetric flasks is in the preparation of standard solutions to be used in volumetric analysis, they are also conveniently employed in the manufacture of liquid pharmaceutical preparations in which it is required that the finished preparation shall be adjusted to a definite volume. For the sake of accuracy, volumetric flasks are usually calibrated "to contain," rather than "to deliver." This is because it is impossible to discharge completely all the liquid contained in a flask or other vessel, if the liquid is one that is attracted by glass, on account of the effect of capillarity. The usual sizes of volumetric flasks include those of 10, 25, 50, 100, 200, 250, 1,000, and 2,000 cc. capacities.

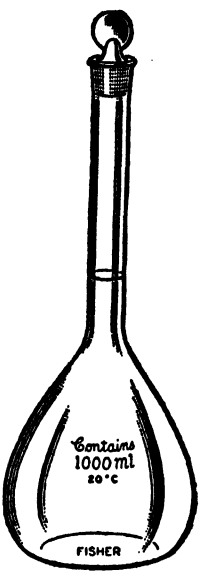
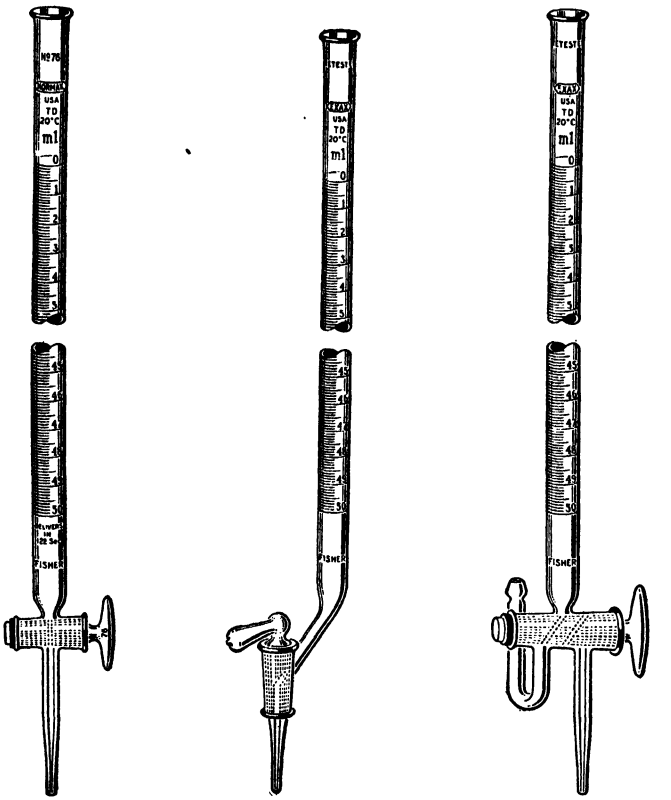


FIG. 22.—Volumetric flask.

Burettes.—Burettes are used for the purpose of accurately measuring the volume of a solution of known strength required to react chemically with a known weight of a substance of unknown purity in volumetric analysis. This operation is commonly called **titration.** The instrument for such measurements, known as a burette, consists of a narrow tube of nearly uniform diameter, graduated in cubic centimeters and fractions thereof. The burette is also used to deliver a definite volume of a solution of known concentration in dispensing operations. Several forms of burettes are shown in Figs. 23*a*, *b*, and *c*.

All except the dispensing burette are manufactured in 25, 50, and 100 cc. capacities. The dispensing burette may be obtained in various sizes, varying in total capacity from 250 to 1,000 cc. The three-way stopcock burette is designed to permit easy refilling by means of a reserve supply of the solution contained in a

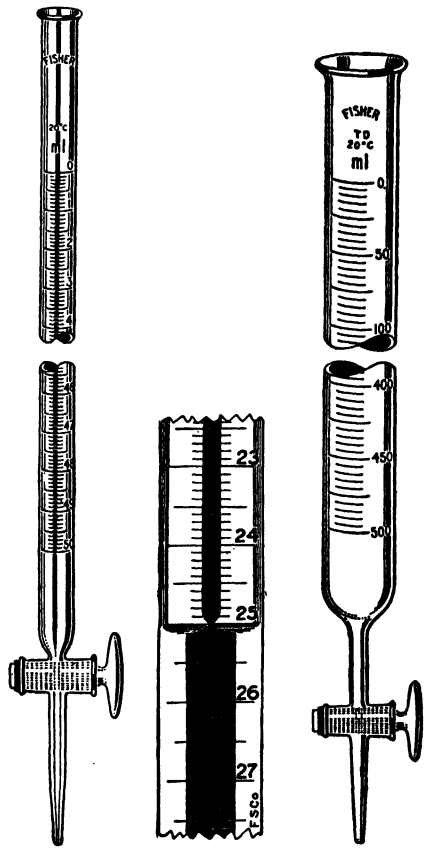


Straight burette. Bent burette. Three-way stopcock burette.

FIG. 23*a*.—Burettes.

flask in an elevated position. The Schellbach burette is specially designed partly to overcome the danger of improper reading of the meniscus. The back wall of the burette is provided with a vertical blue stripe, which is magnified by the lens effect of the liquid. At a point above the meniscus no magnification occurs. Such instruments are read at the point of narrowest constriction

of the blue stripe. The Pharmacopoeia provides that all burettes shall be provided with glass stopcocks, except that burettes equipped with rubber tubes, pinchcocks, and glass delivery tubes in place of glass stopcocks may be used for potassium and sodium



Schellbach burette.

Dispensing burette.

FIG. 23*b*.—Burettes.

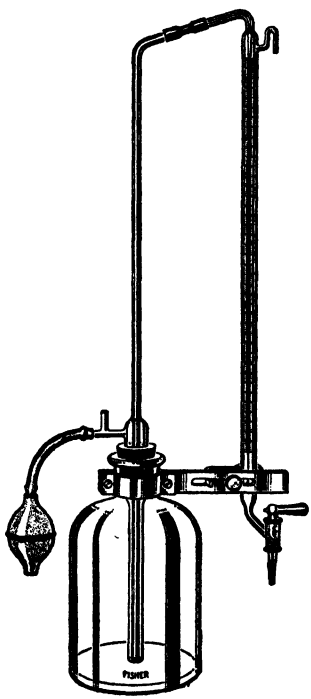
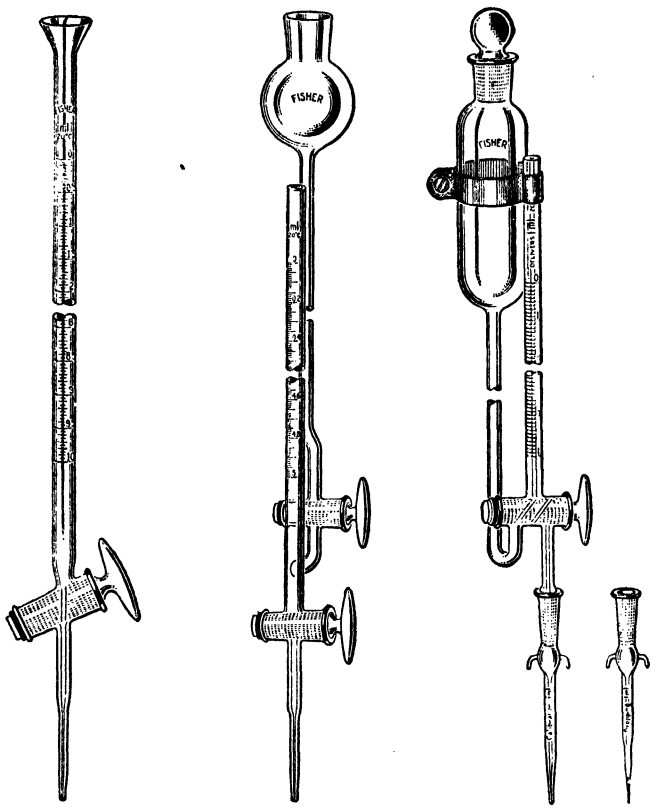


FIG. 23*c*.—Automatic burette.

hydroxide solutions and such other solutions as are best used in this type of burette.

Microburettes.—Reference was made to microanalysis under Analytical Balances, and the need for special balances of extremely high sensitivity for making gravimetric measurements. Since the methods used include volumetric procedures, special

burettes are required for accurate measurement of extremely small volumes of standard solutions. A few of the commonly used microburettes are shown in Fig. 24. The Schellbach microburette contains 10 cc., in 0.05-cc. divisions, and is so



Schellbach microburette. Fisher specifications microburette. Koch microburette.

FIG. 24.—Microburettes.

calibrated that it may be read to 0.005 cc.; it is provided with a funnel top for convenience in filling. The Fisher specifications microburette holds 5 cc. and is calibrated into 0.01-cc. subdivisions. A reservoir of sufficient capacity to fill the burette about ten times is attached to the burette at a point below the graduated

portion by means of a filling tube provided with a stopcock. The Koch microburette has a three-way stopcock and a reservoir used for refilling the instrument. Two interchangeable outlet tips are provided, one for calibration and the other for adjusting the delivery to 100 to 110 drops per cc. Burettes of this type are manufactured in 1, 2, 5, and 10 cc. capacities. All but the largest size are graduated in 0.01-cc. subdivisions, and in this case the smallest subdivision is 0.05 cc.

Pipettes.—Pipettes usually are tubes, either of uniform bore or containing enlarged bulbs, which are used for accurately measuring the volume of liquids. As a rule, they are filled by suction, applied either by the mouth or by a rubber suction bulb. They may be classified into three subdivisions as transfer pipettes, measuring pipettes, and dropping pipettes. All calibrated pipettes are adjusted "to deliver" the indicated volumes, rather than "to contain." Typical forms of transfer and measuring pipettes are shown in Figs. 25*a* and *b*.

As can be seen from the figure, the transfer pipette is intended to measure a definite volume of liquid and therefore has only a single graduation. After being filled, the outside surface of the delivery tube should be wiped free of adhering liquid, the liquid being retained by placing the tip of the forefinger over the upper opening of the pipette. As the liquid is allowed to flow out of the tube, the tip of the pipette is touched against the beaker, flask, or other receiver. Under no circumstances is the last drop to be removed by blowing through the pipette, for this will involve an error in the volume of liquid delivered. The tip of the pipette is held in contact with the glass surface of the receiving vessel when it is calibrated, and the same procedure must be observed in its use. Transfer pipettes may be obtained in smaller sizes, especially for microchemical analysis, but the usual sizes are 1, 2, 5, 10, 25, 50, 100, and 200 cc.

Measuring pipettes resemble burettes in that they are graduated to permit the delivery of any desired volume within the capacity of the instrument. The usual sizes of measuring pipettes include those of 1, 5, 10, 25, and 50 cc. capacities. Ordinarily, the smallest subdivision shown is 0.1 cc.; however, a 1-cc. pipette may be obtained that is graduated in 0.01-cc. subdivisions.

Dropping Pipettes.—These instruments consist of small tubes of uniform diameter, drawn to a tip at the lower end and fitted with a rubber suction bulb for filling and expelling the liquid. Except for types designed for special uses, such as the micro dropping pipette, they are ungraduated. The measurements are made by counting the number of drops of a liquid that are

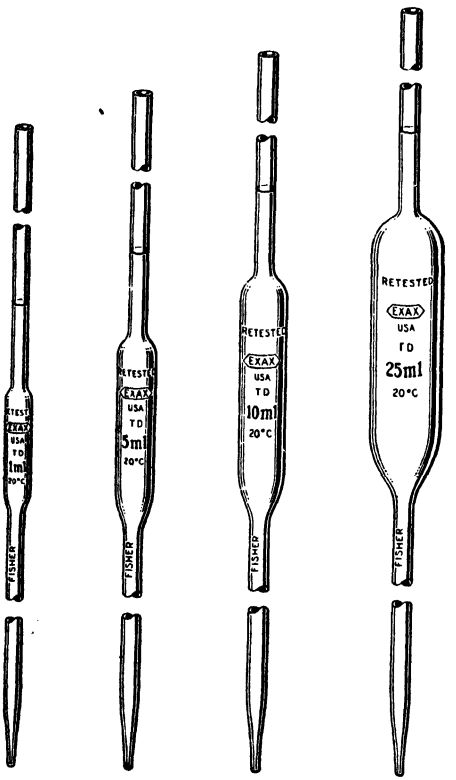


FIG. 25*a*.—Transfer pipettes.

dispensed. For reasons given under Standard Droppers, which follows, dropping pipettes are not to be regarded as instruments of high precision, but they are conveniently used in transferring small volumes of liquid where accurate measurement is of no particular importance.

Standard Droppers.—Earlier in this chapter, in the discussion of the United States fluid system, mention was made of the

fallacy of confusing the drop of a liquid with the minim. The size of a drop of any liquid may vary widely, since the factors that determine its size are numerous. In general, it may be said that these factors are the surface tension of the liquid, its specific gravity, the temperature, the shape and dimensions of the surface

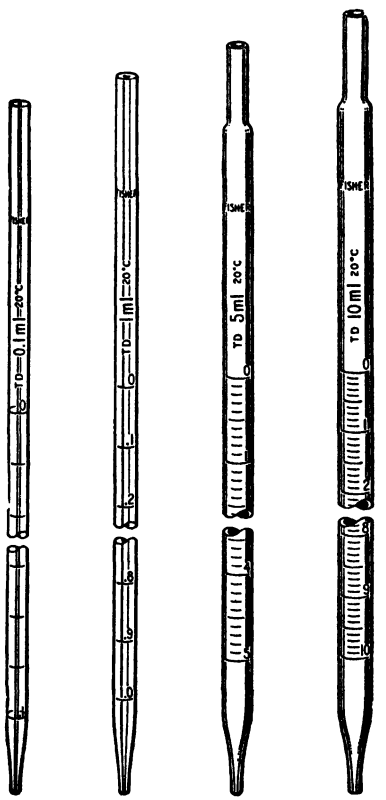


FIG. 25*b*.—Measuring pipettes.

from which the drop is formed, and the pressure or rate of flow of the liquid. Thus, it can be seen that, for a given liquid, the size of the individual drop may be standardized only by controlling all these factors.

The influence of the shape and dimensions of the surface from which the drop is formed may be easily demonstrated by comparing the size of a drop of water formed by the ordinary dropping pipette with that produced when water is permitted to drip from

the undersurface of a large beaker or round-bottom flask. When a liquid drips from a tube, if the liquid is one which wets glass, it has been found that it is the external diameter of the tube which controls the size of the drop, rather than the bore of the tube. This is because the liquid is held temporarily by capillary attraction between the liquid and the glass, and the force of this attraction depends upon the total area represented by the end of the tube. If the external dimensions of the tube are increased, the

Curved medicine dropper. Straight dropping pipette. Large dropping pipette. Micro dropping pipette.

FIG. 26.—Dropping pipettes.

drops will be larger. It is only when the force of gravity overcomes the opposing force of capillary attraction that the drop is formed.

An effort has been made by the Pharmacopoeia, in the twelfth revision, to standardize the dropping pipette in order to regulate the size of the drop. Under the heading Official Medicine Dropper, page 594, the official medicine dropper is described as one having its delivery end 3 mm. in external diameter, and adjusted to deliver 20 drops of water, weighing 1 Gm., at a temperature of 15°C. A tolerance of 10 per cent below or above the specified number of drops, corresponding to 18 and 22 drops per Gm., respectively, is permitted.

It will be noted that the number of drops which such a standard dropper will deliver is based upon the behavior of water and that

this value cannot be interpreted as applying to other liquids. The addition of even small proportions of a solute to water so modifies its surface tension that the number of drops per gram yielded by the standard dropper may be changed appreciably. If the drop is to be used as a unit of measurement for any liquid other than water, the only safe procedure is to determine the number of drops obtained with a given dropper by a determination of the number of drops yielded per cubic centimeter of the liquid and use this factor as a guide in dispensing the desired volume.

Care and Use of Glass Measures.—Measures and other glass apparatus should be kept clean. This may be accomplished in a number of ways. The most effective and least dangerous method is to wash with hot soapy water or water containing one or more of the modern detergents such as the alkali phosphates. Rinse the container with distilled water, preferably hot, and allow it to dry by inverting on a rack and draining. If a clean container is not secured in this manner, more rigorous treatment must be applied. This is obtained by the so-called "cleaning solutions" (see "The Pharmaceutical Recipe Book III," pages 404 to 405), which include dichromate–sulfuric acid solutions, or concentrated sulfuric acid, to which a small amount of concentrated nitric acid has been added. The former solution is usually effective at room temperature if allowed to stand for a time in contact with the container, or it may be immediately effective when hot and must then be used with caution to avoid severe acid burns. The latter solution when heated is especially useful in cleaning containers contaminated with organic residues.

Dry containers may be procured by (1) rinsing with hot water and inverting the vessel, (2) blowing or drawing clean air through the apparatus, (3) placing in a drying oven, and (4) using a clean, soft towel, preferably one that has been laundered to remove fillers and linters, which streak the glassware. Quick drying may be accomplished by rinsing the container with acetone or by rinsing with alcohol to remove surplus moisture, followed by a rinse of ether.

STUDY QUESTIONS

1. What is the meaning of the term *metrology*?

2. Name some examples of units for measuring distances that are based upon parts of the human body.

3. What is the origin of the term *grain* as the name of a unit of weight?

4. To whom is credit for the origin of the metric system usually assigned?

5. What is the primary standard from which all metric units are theoretically derived?

6. What is the actual standard that is used for the derivation of all metric units?

7. What is the standard unit for weight in the metric system, and how is it derived?

8. What is the primary unit for volume in the metric system, and how is it derived?

9. Distinguish between weight and mass.

10. What differences are noted in the weight of objects when weighed at different locations on the earth's surface, and how are these differences explained?

11. For what kind of transactions is the troy system used?

12. When is the apothecaries' weight system used?

13. What is the application of avoirdupois weight to pharmacy?

14. What relationships exist among the troy grain, the apothecaries' grain, and the avoirdupois grain?

15. What is the standard unit of the United States fluid system, and how is it defined?

16. What relationship, if any, exists between the minim and the drop?

17. Tabulate the five fundamental equivalents required to make conversions of the units of the various systems for weight and volume.

18. Convert 987 Gm. into proper units of the apothecaries' system.

19. Convert 743 Gm. into proper units of the avoirdupois system.

20. What is the equivalent in the metric system for the following quantity: 3 lb., 6 ℥, 3 ʒ, 2 ℈, 10 gr. (apoth.)?

21. Convert the following quantity, expressed in the apothecaries' system, into proper units of avoirdupois weight: 4 lb., 7 ℥, 2 ʒ, 2 ℈, 10 gr.

22. Convert the following quantity, expressed in avoirdupois weight, into metric weight: 3 lb., 11 oz., 112 gr.

23. What is the equivalent in the apothecaries' system for 2 lb., 5 oz., 315 gr. (av.)?

24. Calculate the equivalent volume, in proper units of the United States fluid system, for 8,473 cc.

25. What is the equivalent volume in the metric system for 2 gal., 1 pt., 4 f℥, 2 fʒ, and 30 ♏?

26. Explain the principle of moments as applied to the beam-type balance.

27. Define the zero point of a balance, and explain how it is determined.

28. Define the sensitivity of a balance, and explain how it is calculated.

29. Explain the principle upon which the operation of the torsion balance depends.

30. What advantages are claimed for the Ainsworth keyboard analytical balance?

31. What are the special advantages of analytical balances employing a gold chain as a substitute for the rider?

32. What is the principle involved in the use of the magnetic damping device, and what purpose does it serve?

33. Upon which balance pan should the object to be weighed be placed, and why?

34. Explain the procedure followed in the so-called "triple-check" method of computing the sum of the weights used for a weighing.

35. What are the preliminary inspections and tests that should be carried out before undertaking a weighing with the analytical balance?

36. What is the standard temperature for measuring the volume of liquids adopted by the Pharmacopoeia?

37. What is the standard temperature for volume measurements of liquids adopted by the National Bureau of Standards?

38. Distinguish between the transfer and the measuring pipette.

39. Describe the proper procedure to be followed in emptying a pipette.

40. What are the specifications for the official medicine dropper of the Pharmacopoeia, and what purpose does it serve?

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CHAPTER VIII

THE PHYSICAL PROPERTIES OF MATTER

A knowledge of the physical properties of drugs, chemicals, and preparations is of fundamental importance to the pharmacist. These properties are governed by the laws of physics, and much of the work in a beginning course in pharmacy consists in the study and application of these laws to substances of pharmaceutical interest. Among the physical properties to be discussed in this chapter are the following: specific gravity, specific volume, viscosity, refractive index, optical rotation, colorimetry, surface tension, and capillarity. Other physical properties, such as melting points, congealing points, and boiling points, are discussed in Chap. X. Another physical property, solubility, is discussed in Chap. XII.

DENSITY AND SPECIFIC GRAVITY

The specific gravity of a substance may be defined as the ratio of the weight of that substance to the weight of an equal volume of some other substance taken as a standard of comparison. The standard usually selected for solids and liquids is distilled water, and either air or hydrogen is used for comparison with gases. Since in pharmacy we are concerned especially with the specific gravity of solids and liquids, specific gravity may be defined for our purposes as the ratio of the weight of a substance to the weight of distilled water having the same volume as that of the substance. Ordinarily, the comparison is made at the same temperature, but this is not necessarily the case. The Pharmacopoeia defines the standard temperature as 25°C., and, unless otherwise stated, all specific gravities given there are based on this temperature. Frequently, expressions such as (25°/25°), (25°/15°), (15°/4°) are used to indicate the temperature conditions under which the estimation is made. The numerator shows the temperature of the determined substance and the denominator the temperature of the water used for comparison.

Density.—The term *density* is defined as the ratio of the mass of a substance to its volume. This may be expressed by the formula $D = M/V$, in which D is density, M is mass, and V is volume. Theoretically, density may be expressed in any system of weights and measures, but it is usually expressed in the metric system, as grams per cubic centimeter, or Kilograms per liter. If expressed in this way, it is apparent that all true densities would actually be based upon a comparison with the weight of an equal volume of water at a temperature of 4°C., since the gram is defined as the weight of 1 cc. of distilled water at 4°C. It should also be noted that, as was pointed out in Chap. VII, weight is not identical to mass, but proportional to it. Theoretically, specific gravity can be determined at any desired temperature, while the temperature of the standard for all density determinations is limited to 4°C. Because of this fact, specific gravity is widely used in pharmacy, although the term *density* is frequently encountered in physics and chemistry.

Applications of Specific Gravity.—A thorough understanding of specific gravity is of particular importance in pharmacy for the following reasons:

Since specific gravity is a physical property of matter, it serves as an indication of the identity of many substances.

It also affords a convenient method for ascertaining the purity and strength of many substances, particularly of liquids.

It permits the pharmacist to calculate the weight of a given volume of liquid or, conversely, the size of the container required to hold a given weight of a liquid.

Principle of Archimedes.—Many of the methods for determining specific gravity are based upon the principle of Archimedes. It is essential to understand this principle thoroughly before determinations of specific gravity are attempted. It may be briefly stated as follows: **A body placed in a liquid is buoyed up by a force equal to the weight of the displaced liquid.** Since the applications of this principle deal with two kinds of bodies, namely, those which float and those which sink upon being placed in a liquid, it may be more readily understood if restated as follows: (1) **A floating body sinks to a sufficient depth in any liquid to displace its own weight of that liquid.** (2) **A sinking body, when immersed in a liquid, undergoes a loss in weight**

equal to the weight of liquid displaced. It should be noted that these principles apply to all liquids and all gases, not for distilled water alone. Failure to appreciate this fact sometimes leads to confusion in the mind of the student. It should also be noted that the term *immersed* means to be completely submerged beneath the surface of the liquid. With the exception of the use of the pycnometer, or specific-gravity bottle, all methods of determination of specific gravity of pharmaceutical application depend upon the principle of Archimedes. These applications will be made as the various methods are discussed.

Specific Gravity of Liquids.—The methods most commonly employed in the determination of the specific gravity of liquids are as follows: the pycnometer method; the plummet, or sinker, method; the use of the Westphal balance; the use of hydrometers of various types and of Lovi's beads.

Pycnometer Method.—The pycnometer (from *pykno*, meaning close, compact, dense, and *meter*, meaning measure) is a small flask having a ground-glass stopper provided with a small capillary opening, so arranged that it may be completely filled with liquids, thus ensuring an accurate means of comparing the weights of equal volumes. Another name sometimes used for certain types of pycnometer is specific-gravity bottle. Before the pycnometer is filled, its tared (pronounced *târd*) weight (weight when empty) is determined. Then by completely filling the pycnometer, first with distilled water and then with the liquid to be tested, the net weights of equal volumes of the two liquids are obtained by subtracting the tare from the gross in each case.

Since specific gravity is the ratio of the weight of the substance (in this case a liquid) to the weight of an equal volume of water, the specific gravity of the liquid is obtained by dividing the weight of the liquid by the weight of an equal volume of water.

Pycnometers may be obtained in various sizes ranging from 5 to 100 cc. in capacity. The size most commonly used for ordinary determinations is 25 cc. Several varieties of pycnometer are available, such as those provided with caps which fit over the stopper in order to prevent loss in weight due to evaporation of the liquid being tested. Others are provided with a side-arm capillary tube and a thermometer, which is fitted with a ground-glass connection into the neck of the pycnometer and used for the

purpose of determining the temperature of the liquid while it is actually being weighed. Still another variation is the pycnometer provided with a vacuum jacket, made with double walls and having the air partly exhausted. This arrangement is for the purpose of heat insulation and tends to guard against changes in temperature and consequent changes in volume while the determination is being made. It should be noted that this method differs from all others applied to the determination of the specific gravity of liquids in that the weights of the equal

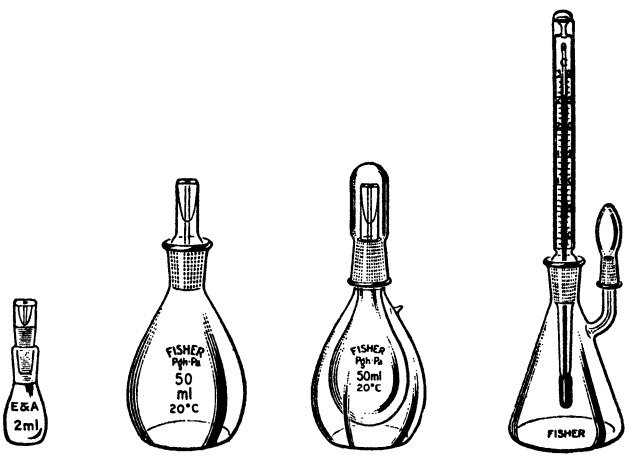


FIG. 27.—Pycnómeters.

volumes of liquids that are being compared are obtained by direct weighings.

Although from the standpoint of accuracy a pycnometer is desirable, it is possible to make use of this method even if a pycnometer is not available. Any container graduated to contain a definite volume of liquid, such as a volumetric flask, a conical or cylindrical graduate, or even a prescription bottle of suitable size, may be used for this purpose.

The calculation of the specific gravity by the pycnometer method is illustrated in the example that follows:

An empty pycnometer weighs 18.452 Gm. When it is filled with alcohol, the total weight is 38.702 Gm.; when it is filled with distilled water, the total weight is 43.452 Gm. Calculate the specific gravity of the alcohol.

Alcohol	Distilled Water
38.702 Gm. (gross)	43.452 Gm. (gross)
18.452 Gm. (tare)	18.452 Gm. (tare)
20.250 Gm. (net)	25.000 Gm. (net)

$\frac{20.250}{25.000} = 0.810$, specific gravity of the alcohol.

Sprengel Tube.—The Sprengel tube is essentially a modification of the pycnometer, or specific-gravity bottle, intended for use when the supply of liquid to be tested is limited. The usual form is that of a U tube made of capillary tubing, provided with bulbs on both side arms for the purpose of increasing the capacity. The ends of the tubes have caps fitted with ground-glass joints to prevent loss by evaporation. The arms of the tube are provided with marks that permit accurate measurement of the volume of the liquid being weighed. As a rule, the tube is weighed while suspended from the stirrup of the balance by a platinum wire. The liquid is introduced into the tube by means of suction. The weighings that are necessary and the method of calculation are identical with those used in the pycnometer method.

Nicol Tube.—Another modification of the pycnometer, or specific-gravity bottle, is the Nicol tube, which closely resembles the Sprengel tube but

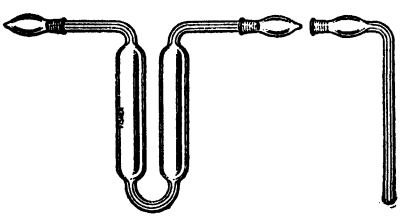


FIG. 28.—Sprengel tube.

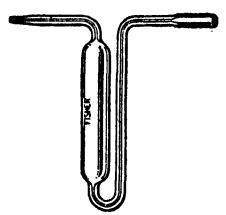


FIG. 29.—Nichol tube.

which, as can be seen from Fig. 29, differs from the latter in that it contains a bulb in one side arm of the U tube only. It is used in exactly the same way as the Sprengel tube.

Plummet, or Sinker, Method.—To make determinations of specific gravity by the plummet, or sinker, method, it is necessary to use a hydrostatic balance. This is nothing more than a balance so arranged that a sinking body may be weighed while immersed in a liquid, the liquid in question being supported independently of the balance pan. This may be done with an ordinary balance in several ways. The equal-arm trip balance may, for example, be mounted on a ring stand. A hook will be found on the lower side of the left arm of the beam to which the sinker may be attached by means of a fine thread. Any weight attached at this point has the same effect as if it were placed upon the left-hand platform, or pan, of the balance. The beaker or other utensil containing the liquid to be tested is placed on

the table beneath the balance. For the equal-arm balance equipped with balance pans suspended from the beam, a small benchlike support is used, which is wide enough to straddle the balance pan and high enough to permit the movement of the pan without interference. The beaker or other container for the liquid is placed on this support, and the object to be weighed hydrostatically is suspended by a fine thread from the stirrup at the left end of the beam. In making hydrostatic weighings, adjustments must be made to permit the full swing of the balance without causing the object to break the surface of the liquid or strike the bottom of the container. If the object is permitted to rise above the surface, its weight immediately changes

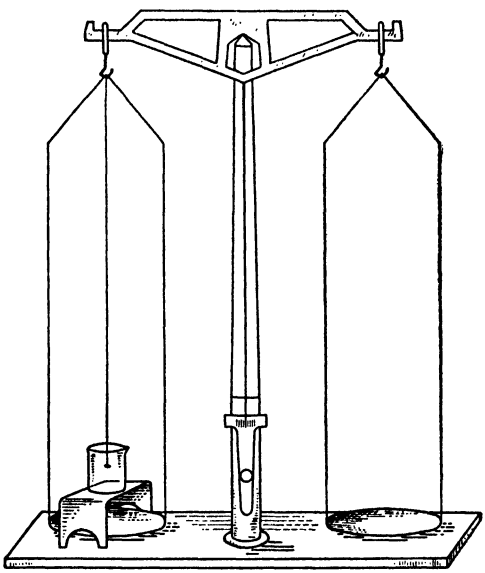


FIG. 30.—Hydrostatic balance.

because of decrease in the buoyant effect of the liquid, since less liquid is being displaced. Weighings made under these conditions by the inexperienced operator are a frequent source of error in the determination of specific gravity by this method.

The application of the plummet, or sinker, method may be illustrated by the following example: A 20-Gm. brass weight taken from a set of weights, when weighed hydrostatically in water, shows a weight of 17.62 Gm. When the same object is weighed hydrostatically in alcohol, its weight is found to be 18.07 Gm. Since the weight of the object in air is 20 Gm., subtraction will show the loss in weight (the buoyant effect) for each liquid. Thus, it is found that the brass weight loses 2.38 Gm. in water and 1.93 Gm. in alcohol. Since, according to Archimedes' principle, a solid when immersed in a liquid suffers a loss in weight equal to the weight of the liquid displaced and since

it is safe to assume that the brass weight did not undergo any appreciable change in volume due to the pressure of the liquids, it must follow that the losses in weight represent the weights of equal volumes of the two liquids. Since specific gravity, in this case, is the ratio of the weight of alcohol to the weight of an equal volume of water, this may be calculated by dividing the loss in weight in alcohol (1.93 Gm.) by the loss in weight in water (2.38 Gm.) to obtain 0.81 (the specific gravity of alcohol). This means that a given volume of alcohol has a weight of only 0.81 times as great as the weight of the same volume of water or that a pint of alcohol weighs only 0.81 as much as a pint of water.

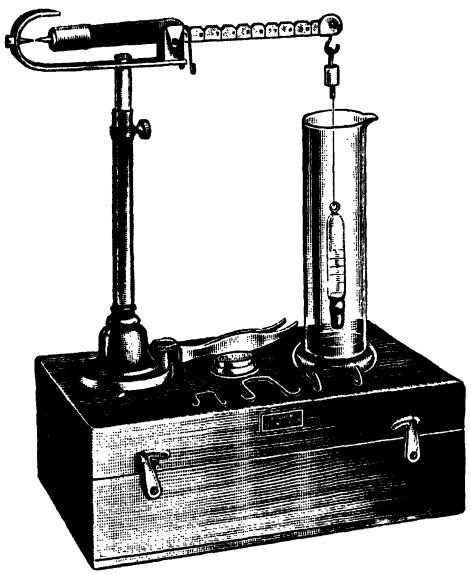


FIG. 31.—Westphal balance.

Westphal Balance.—An application of the plummet, or sinker, method that is extremely convenient for use in the determination of specific gravity of liquids is represented by the Westphal specific-gravity balance. This instrument, as can be seen from Fig. 31, consists of a specially devised beam mounted upon a bracket, which in turn is supported by an adjustable pillar. The beam is provided with a counterpoise for the plummet and an index pointer at one end. The other arm of the beam is subdivided into nine notched and numbered divisions and has a pivoted hook at the end for the suspension of the plummet.

The plummet consists of a weighted glass tube having an enclosed thermometer and so adjusted in weight that it will displace exactly 5 Gm. of water at a temperature of 15.5°C. and weigh exactly 15 Gm. in air. The balance is provided with a set of weights of special design in the form of loops with a hook at each end. This arrangement permits the suspension of two or more weights from the same notch of the beam. There are four sizes of weights, having values of 5.0, 0.5, 0.05, and 0.005 Gm., respectively.

Since the weight of the plummet in air is exactly balanced by the counterpoise at the other end of the beam, immersion of the plummet in a liquid permits a direct measurement of the buoyant effect of the liquid being tested. Thus, if immersed in water, the plummet will displace 5 Gm. of water. In order to reestablish equilibrium, it will be found necessary to place one of the largest weights (5.0 Gm.) upon the terminal hook corresponding to the last position on the numbered scale. This means that the specific gravity of the liquid being tested is 1.0. Since, in the testing of any liquid, the relative positions of the weights on the beam are proportional to the buoyant effect of water upon the plummet, no calculations are necessary. By reading the numbered positions of the weights in the order of decreasing size and supplying zeros where a given size in the series is omitted, the specific gravity may be read directly. It is unfortunate that the temperature selected for the standard value in the use of the Westphal balance is 15.5°C. in view of the fact that the standard temperature of the Pharmacopoeia is 25°C., since, for absolute accuracy, all liquids must be adjusted exactly to this temperature (15.5°C.) before being tested. The selection of this temperature is based on the fact that the instrument was primarily designed for testing the specific gravity of alcoholic solutions and this temperature approximates the one adopted by the Treasury Department in computing the proof gallon, which is the basis for the Federal tax on alcohol.

The Use of Hydrometers.—One of the most convenient and rapid methods for determining the specific gravity of liquids is the hydrometer method. The hydrometer consists of a floating instrument usually made of glass and weighted with mercury or lead pellets at one end so that it floats upright in the liquid. In

general, hydrometers may be divided into two classes, (1) those having constant weight with variable volume and (2) those having constant volume with variable weight. Of the two classes, the first is the more important, since it is the more widely used. The constant-level hydrometer and Nicholson's hydrometer, mentioned later in this chapter, are examples of the second class. An instrument of the constant-weight type is provided with a long stem extending from the central bulb and graduated in such a way that the specific gravity may be read directly or in units of an arbitrary scale, which may be easily converted into specific gravity by application of the appropriate formula. In order to make the reading, a sufficient quantity of the liquid to be tested is placed in a cylindrical container, and the hydrometer is allowed to seek its level in the liquid. Just as in reading the graduate or burette, the point on the scale indicated by the lowest point of the meniscus is read. Many hydrometers are equipped with a thermometer, which serves to show the temperature of the liquid being tested. The temperature at which the hydrometer was standardized is usually marked upon the instrument.

Hydrometers designed for special uses have been given special names, such as alcoholometers (used in the determination of the specific gravity of alcoholic solutions), lactometers (used for milk), saccharometers (for sugar solutions), and urinometers (for urine). Other hydrometers have been provided with special scales such as the **American Petroleum Institute** scale, the **Baumé,** the **Brix,** the **New York Board of Health** lactometer scale, the **Quevenne** lactometer scale, and the **Twaddell** scale. A combination frequently met with shows the Baumé scale with the regular specific-gravity scale.

Although the hydrometer method is most convenient to use, it has a disadvantage in that a considerable volume of the liquid is required in order to float the instrument. The actual volume required varies considerably, depending upon the style and length of the instrument being used.

Regardless of the type of hydrometer, all determinations involving its use are based on the principle of Archimedes that applies to the behavior of floating bodies: **A floating body is buoyed up by a force equal to the weight of the liquid displaced.**

The graduation of the hydrometer is easily accomplished by noting the position at which the instrument floats in two liquids of known specific gravities. The liquids selected should differ widely in specific gravity so that a greater range may be covered.

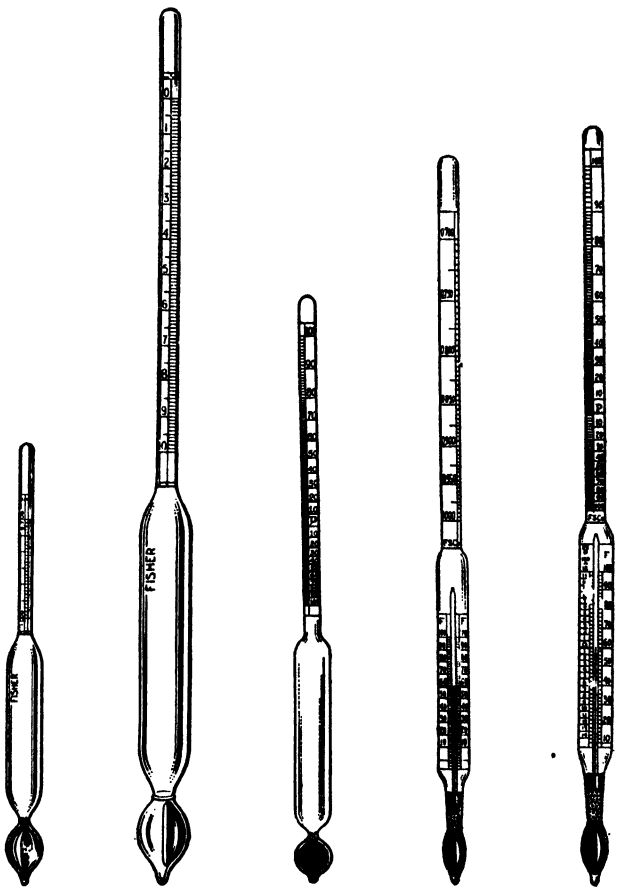


FIG. 32.—Hydrometers.

Upon determining the positions on the stem of the hydrometer for the two liquids of known specific gravity, the scale is extended along the stem of the instrument in proportion to the determined values.

Constant-level Hydrometer.—A variation from the hydrometer having a scale was the older type provided with a single mark on the stem. By the

addition of weights, which were usually placed on a platform at the upper end of the hydrometer stem, the instrument was forced to sink to a constant depth as indicated by the single graduation on the stem. A comparison of the weight required to submerge it to this point in a given liquid, as compared with the weight required to effect the same displacement in water, formed the basis for the calculation of specific gravity. This instrument offered no advantage over the use of the hydrostatic balance except that the constant-level hydrometer replaced the balance in this determination.

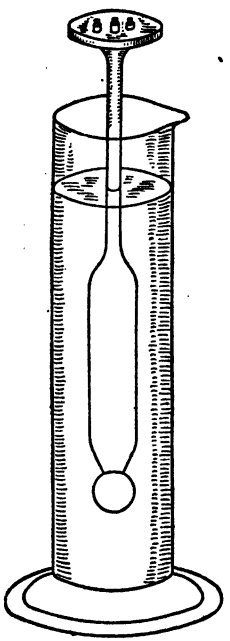


FIG. 33.—Constant-level hydrometer.

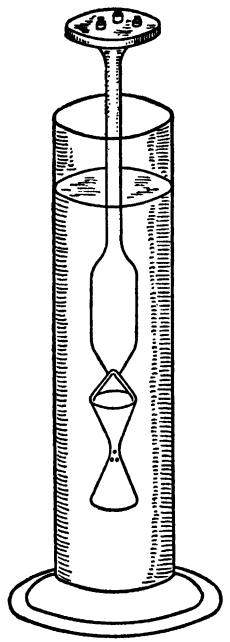


FIG. 34.—Nicholson's hydrometer.

Nicholson's Hydrometer.—A further modification of the principle of the constant-level hydrometer is represented by Nicholson's hydrometer, which was adapted for use in determining the specific gravity of solids as well as liquids. A special container consisting of two cones was attached to the lower end of the instrument. The lower cone having the apex upward was used to force floating bodies beneath the surface of the water. The upper cone with its apex pointing downward was used for weighing objects heavier than water while immersed. By noting the weight of a solid in air and the difference in weights required to adjust the hydrometer level to the mark when tested with and without the solid whose specific gravity was being determined, the buoyant effect (loss in weight in water) could be obtained.

This value divided into the weight of the body in air gave the specific gravity of the solid.

Special Types of Hydrometers.—A wide variety of hydrometers has been developed for special uses. In many cases they have been given characteristic names, and frequently arbitrary scales have been adopted bearing no direct relationship to specific gravity. Space does not permit a detailed discussion of all these. Only those of special importance, or of particular interest to pharmacists, will be described.

Alcoholometers.—Hydrometers especially designed for use in determining the strength of alcoholic solutions are called alcoholometers. These instruments are graduated in the **Tralle** scale, in which the reading in degrees corresponds in numerical value with the percentage of alcohol by volume at 15.56°C. (60°F.). This particular temperature is used because of the fact that the government tax on alcohol in alcoholic beverages is based upon the proof gallon, which is one U.S. fluid gallon of 100 proof spirit, or its equivalent, taken at the temperature of 15.56°C. A strength of 100 proof corresponds to 50 per cent by volume. A special type of alcoholometer, known as the **wine and must hydrometer,** has three scales, one of which reads from 0 to 30° Brix (see the Brix scale under Saccharometers) and is used for determining the percentage of sugar present in wine. A second scale extends from 0 to 15° Tralle and is used for testing sweet wines; the third scale is used for the testing of tart (dry) wines and covers the range from 0 to 20° Tralle.

Baumé Hydrometers.—The hydrometers devised by Baumé consist of two instruments, one called the **pèse-esprit,** for liquids lighter than water, and the other the **pèse-acide** or **pèse-sirop,** for liquids heavier than water. The instrument for light liquids is standardized by immersing in a 10 per cent (by weight) aqueous solution of ordinary salt and in water. The point to which the hydrometer sinks in the salt solution is marked 0, and the level shown in water is marked 10. The scale is then extended proportionately along the stem of the instrument. In order to derive the specific gravity for the observed reading, the following formula is used:

$$\text{Specific gravity} = \frac{140}{130 + \text{degrees light Baumé}}$$

Conversely, if the specific gravity of a liquid lighter than water is known, the corresponding reading in Baumé degrees light may be obtained by use of the following formula:

$$\text{Baumé degrees light} = \frac{140}{\text{sp. gr.}} - 130$$

The instrument designed for use with liquids heavier than water is standardized by placing it in a 15 per cent (by weight) solution of salt and in water. The level shown in water is marked 0 and that shown in the salt solution 15, and the scale is extended accordingly. The formula for conversion to specific gravity is the following:

$$\text{Specific gravity} = \frac{145}{145 - \text{degrees heavy Baumé}}$$

The corresponding reading in Baumé degrees heavy may be obtained for a given specific gravity (of a liquid heavier than water) by substituting its value in the following formula:

$$\text{Baumé degrees heavy} = 145 - \frac{145}{\text{sp. gr.}}$$

American Petroleum Institute Scale.—A modification of the Baumé instrument for liquids lighter than water that is approved by the Bureau of Standards uses the special scale adopted by the American Petroleum Institute. This instrument is used exclusively in the testing of gasoline and petroleum products. The usual type carries a scale extending from 10 to 45°. A special formula must be used for conversion of the observed readings to specific gravity, which is as follows:

$$\text{Specific gravity at 60°F. (15.56°C.)} = \frac{141.5}{131.5 + \text{degrees light Baumé}}$$

The Twaddell Scale.—Another instrument that is used only for liquids heavier than water is the Twaddell hydrometer. This instrument is provided with a scale so designed that the observed reading, if multiplied by 5 and added to 1,000, is the specific gravity with reference to water taken as 1,000 at 60°F. Conversely, if specific gravity is to be converted into Twaddell degrees, the decimal portion of the specific gravity is multiplied by 200. Thus, a specific gravity of 1.048 would correspond to

$$0.048 \times 200 = 9.6 \text{ deg. Twaddell}$$

Lactometers.—A hydrometer designed especially for determining the specific gravity of milk is called a lactometer. This instrument is used, either alone or, more frequently, in conjunction with butterfat determina-

tions, in judging the quality of milk. The two most widely used instruments are the New York Board of Health lactometer and the Quevenne lactometer. The former is graduated in degrees extending from 0 to 120. The 0° reading corresponds with the level to which the instrument sinks in water, while the reading of 100° is equivalent to a specific gravity of 1.029, which is considered to be the minimum specific gravity for a normal sample (unadulterated with water). Thus, a sample showing a reading less than 100° is regarded as falling below the minimum value for unadulterated milk. Conversions from the lactometer readings to specific gravities may be made by the following formula:

$$\text{Specific gravity} = 1.000 + \frac{L \times 0.029}{100}$$

in which L represents the lactometer reading in degrees. Thus a reading of 120° would be equivalent to

$$1.000 + \frac{120 \times 0.029}{100} = 1.0348 \text{ (sp. gr.)}$$

The Quevenne lactometer is graduated in degrees extending from 15 to 40, which correspond to the specific gravities of 1.015 and 1.040, respectively.

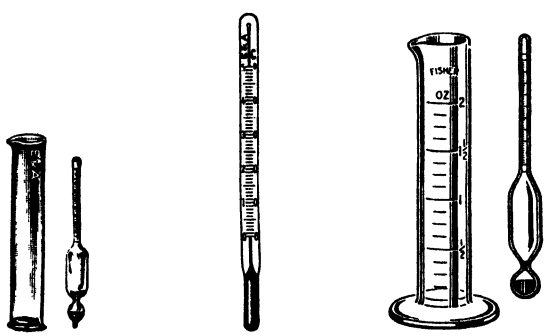


FIG. 35.—Urinometers.

It can be seen that the values are merely abbreviated forms for the specific gravities in which the figures in the second and third decimal places (the significant values) are used as whole numbers. Degrees of the New York Board of Health lactometer may be converted into Quevenne degrees by multiplying by 0.29. Both instruments are adjusted for use at a temperature of 60°F. (15.56°C.).

Saccharometers.—The instrument especially adapted for use in determining the concentration of sugar solutions is known as a saccharometer. The most widely used instrument of this type is the Brix saccharometer. This finds application in sugar refining, brewing, and the production of wines. The degrees of the Brix scale correspond to the percentage by weight of cane sugar in solution, when used at the temperature indicated on the instrument.

Urinometers.—The instrument designed especially for the determination of the specific gravity of urine is called a urinometer. Since the usual range in clinical specimens may extend from a specific gravity approaching 1.000 to a maximum of 1.060, they are usually graduated to cover this range. In order to obtain greater accuracy, three instruments are sometimes used, showing ranges of 1.000 to 1.020, 1.020 to 1.040, and 1.040 to 1.060, respectively. On some urinometers only the last two figures of the specific gravity are shown on the scale. In such a case, a reading of 20 would correspond to a specific gravity of 1.020. A special type of urinometer is designed for use with small samples (10 cc.) and closely resembles the familiar storage-battery hydrometer. It consists of a hydrometer tube enclosed in a larger tube chamber to which a rubber bulb is attached for the purpose of filling the tube and discharging the sample after the reading has been made. This type of instrument is particularly convenient when a large number of samples are to be tested at one time.

Lovi's Beads.—A convenient method for determining the specific gravity of liquids, which is used especially in certain industrial processes, such as the manufacture of mineral acids, is the use of Lovi's beads. These are sets of glass beads adjusted to different densities by the varying weights of mercury that they contain. The specific gravities of the individual beads are etched on the outside surfaces. In use, an assortment of beads, covering the proper range in specific gravity, are dropped into the liquid to be tested. Some of these will sink immediately to the bottom of the liquid, while others will float. If the series is sufficiently narrow in range, at least one bead should be found that remains suspended indifferently in the liquids, *i.e.*, neither floats on the surface nor rests at the bottom of the container. The specific gravity etched on this bead indicates the specific gravity of the liquid. This is based on the fact that the weight of the bead is in equilibrium with the weight of the liquid displaced, since the bead neither rises nor sinks. Therefore, the specific gravity of liquid must be equal to that of the bead.

The Fisher-Davidson Gravitometer.—A type of instrument employing a new principle in the determination of the specific gravity of liquids has been developed recently and is known as the Fisher-Davidson gravitometer. This apparatus affords a rapid method of determination, since the necessity for all weighings is eliminated, and it is especially useful where only small samples of liquids are available. The specific gravity is read directly from the scale of the instrument, and accurate results

are obtained from samples as small as 0.3 cc. For most organic liquids, changes in temperature have little effect upon the accuracy of the results. The average readings observed at 15 and at 25°C. differ from those obtained at 20°C. by not more than 0.1 per cent. A correction formula for the effect of temperature variations is provided for use with other types of liquids and solutions.

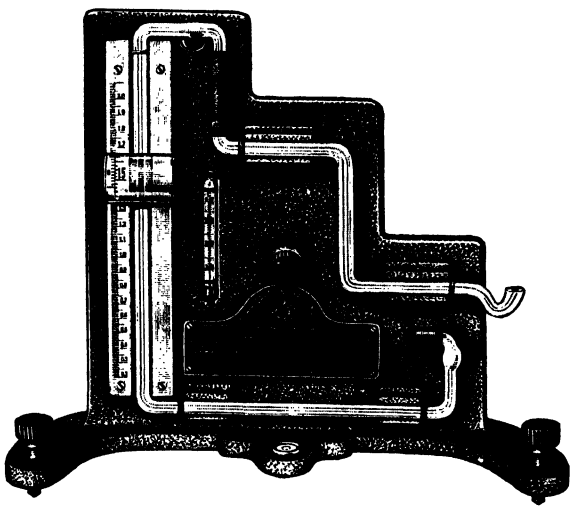


FIG. 36.—The Fisher-Davidson gravitometer.

Experiments have shown that, if two U-tube manometers (instruments used for measuring the pressure of gases and vapors) which are filled with liquids of different densities are connected to a common source of suction, the heights of the two liquids will be inversely proportional to their densities. This may be expressed algebraically as

$$h_1 d_1 = h_2 d_2$$

$$\frac{h_1}{h_2} = \frac{d_2}{d_1}$$

in which h_1 and h_2 represent the heights of the liquids and d_1 and d_2 the densities, respectively, of the two liquids. This shows that, if a liquid of known specific gravity is placed in one U tube, the specific gravity of the liquid in the other tube may be measured.

The two tubes used in the Fisher-Davidson gravitometer are arranged in such a way that the level of the liquid varies in one tube only, which makes a single direct reading possible. One of the tubes is Z-shaped, with an upper and a lower horizontal arm, while the second tube is L-shaped. Both tubes are connected with rubber tubing, and an outlet on the L tube is connected to the pump, which permits a partial vacuum to be applied simultaneously to both tubes.

If liquid is placed in each tube and drawn up by suction until the menisci of the liquid in the Z tube fall within the upper and lower arms, only one variable level need be observed; this is because the horizontal arms of the Z tube ensure a constant height for the liquid contained in that tube that is determined by the span s of the tube, while the L tube provides a fixed lower level for the liquid that it contains. If a reference liquid such as ethylbenzene (sp. gr. 0.867 at 20°/4°) is placed in the L tube, the equation given above becomes

$$h_1(0.867) = sd_2$$

or

$$h_1 = \frac{sd_2}{0.867}$$

If the span s of the Z tube is now made equal to 0.867 unit of the scale attached to the upright arm of the L tube, the equation becomes

$$h_1 = \frac{0.867d_2}{0.867}$$

or

$$h_1 = d_2$$

and a direct reading of the specific gravity of the liquid is made possible. The instrument is calibrated to yield the specific gravity at 20°/4°C.

The scale values shown on the instrument are those established by the use of certified ethylbenzene in the L tube as the standard of comparison. This liquid serves for the determination of all liquids ranging in specific gravity from 0.60 to 2.00. For heavier liquids, the ethylbenzene is replaced by certified carbon tetrachloride (sp. gr. 1.595 at 20°/4°), and in this case the observed scale readings must be multiplied by the factor 1.595/0.867, or 1.84.

For most organic liquids the standard Z tube, having an internal diameter of 1.9 mm., gives satisfactory results. If viscid liquids, such as oils and syrups, are tested in this tube, considerable delay is encountered in the attainment of equilibrium because of their viscosity. For such liquids, the use of a Z tube of 4.0 mm. internal diameter is recommended, and such a tube is supplied with the instrument. Since water and aqueous solutions have a tendency to adhere to the surface of capillary tubes, it is recommended that the 4.0-mm. tubing should be used for testing these liquids. A special tube of 0.8 mm. internal diameter is also available and is recommended for use in testing liquids of low viscosity.

Specific Gravity of Solids.—In determining the specific gravity of solids, the selection of method depends upon a number of factors, such as the physical form of the solid (for example, whether in fine powder or in large pieces), its solubility in water and other liquids, and whether it floats or sinks in the liquid in which it is to be tested. Although the following list of solids does not exhaust the possibilities, it includes those combinations most likely to be encountered in pharmacy.

1. Solids heavier than and insoluble in water.
2. Solids heavier than and soluble in water.
3. Solids lighter than and insoluble in water.
4. Solids heavier than and insoluble in water (in powdered form).

Except for the last class, these determinations are usually made by hydrostatic weighings, which consequently involve the application of the principle of Archimedes.

1. *Solids Heavier Than and Insoluble in Water.*—The most convenient method for determining the specific gravity of solids of this class involves the use of the hydrostatic balance. Two weighings are required, (1) the weight of the object in air and (2) its weight when immersed in water. The following will serve as an example of the calculation required:

A piece of brass weighs 21.84 Gm. in air and 19.24 Gm. when immersed in water. What is its specific gravity? The calculation is made as follows:

Wt. in air	21.84 Gm.
Wt. in water	19.24 Gm.
Loss in wt.	2.60 Gm.

Since, according to the principle of Archimedes, a solid when immersed in a liquid undergoes a loss in weight (is buoyed up by a force) equal to the weight of liquid displaced, the weight of water having the same volume as the piece of brass must be 2.60 Gm. The specific gravity is calculated by dividing the weight of the brass in air by the weight of an equal volume of water (loss of weight in water).

$$\frac{21.84}{2.60} = 8.40, \text{ sp. gr. of brass}$$

2. *Solids Heavier Than and Soluble in Water.*—An example of a solid of this type is potassium alum, $KAl(SO_4)_2 \cdot 12H_2O$, which occurs in the form of large crystals. Because of its solubility in water, it is impossible to obtain an accurate weighing of alum while it is immersed in water, since its weight constantly decreases as it dissolves. If some liquid can be found of which the specific gravity is known or can be determined and in which potassium alum is insoluble, this may be substituted for the water in the hydrostatic weighing. In this case, oil of turpentine (sp. gr. 0.86) will serve, since the alum is insoluble in the oil. The calculation of specific gravity is illustrated by the following example:

A crystal of potassium alum weighs 8.78 Gm. in air and 4.48 Gm. when immersed in oil of turpentine (sp. gr. 0.86). What is its specific gravity?

The loss of weight in oil of turpentine is first calculated.

Wt. of alum in air	8.78 Gm.
Wt. of alum in oil of turpentine	4.48 Gm.
Loss of wt. in oil of turpentine	4.30 Gm.

Since the specific gravity of the oil of turpentine is known to be 0.86 as compared with 1.00 for water, the buoyant effects of equal volumes of the liquids would stand in the same relationship to each other as do their specific gravities. Thus, the theoretical loss of weight of the alum in water would be

$$4.30 \times \frac{1.00}{0.86} = 5.00 \text{ Gm.}$$

and the specific gravity of the alum is obtained by dividing its weight in air by its loss in weight in water (wt. of an equal volume of water).

Thus,

$$\frac{8.78}{5.00} = 1.756, \text{ sp. gr. of potassium alum}$$

3. *Solids Lighter Than and Insoluble in Water.*—The method most commonly used for determining the specific gravity of solids of this class depends upon the use of the hydrostatic balance. A special method has been applied to a few solids lighter than water that does not involve hydrostatic weighings; this will be described later. Because a body that is lighter than water will sink only far enough to displace its own weight of water, it is necessary to use some additional object of sufficient weight and density to force the

lighter body beneath the surface in order that the total buoyant effect (and hence its total displacement) may be measured. Although it is a little surprising at first to learn that a floating body, when forcibly immersed, apparently loses more weight than it possesses, this is perfectly in harmony with the principle of Archimedes as related to sinking bodies, since they are buoyed up by a force equal to the weight of liquid displaced. If the body is lighter than water, naturally the weight of an equal volume of water will be greater than the weight of the body in air.

In order to determine the specific gravity of a body lighter than and insoluble in water, the following weighings are usually obtained: (1) the weight of the object in air; (2) the weight of the sinker in air; (3) the weight of both the sinker and the object while immersed in water; (4) the weight of the sinker alone immersed in water. As will be pointed out later, only three of these weighings are essential to the determination, but the explanation of the calculations can be followed more readily if all four weighings are used. The example that follows will illustrate such a determination.

A cork weighs 9.40 Gm. in air, and a brass weight used as a sinker weighs 50.00 Gm. in air. When the two are attached to each other and weighed while both are immersed in water, the total weight is 14.28 Gm. When the sinker alone is immersed in water, its weight is 44.05 Gm. What is the specific gravity of the cork?

The calculation is made as follows:

$$
\begin{aligned}
&9.40 \text{ Gm., wt. of the cork in air}\\
&50.00 \text{ Gm., wt. of the sinker in air}\\
&\overline{59.40} \text{ Gm., wt. of both in air}\\
&14.28 \text{ Gm., wt. of both in water}\\
&\overline{45.12} \text{ Gm., loss in wt. of both}\\
50.00 - 44.05 = \ &5.95 \text{ Gm., loss in wt. of the sinker}\\
&\overline{39.17} \text{ Gm., loss in wt. of the cork, or the wt. of an equal volume of water}
\end{aligned}
$$

$$\frac{9.40 \text{ (wt. of cork in air)}}{39.17 \text{ (wt. of an equal vol. of water)}} = 0.239, \text{ sp. gr. of cork}$$

As mentioned above, only three weighings are actually needed to determine the specific gravity of solids lighter than and insoluble in water. Accordingly, the example used as an illustration above might be restated as follows:

A cork weighs 9.40 Gm. in air, and a sinker weighs 44.05 Gm. when immersed in water. When they both are immersed in water, the total weight is 14.28 Gm. What is the specific gravity of the cork?

The calculation is made as follows:

$$
\begin{aligned}
&44.05 \text{ Gm., wt. of sinker in water}\\
&14.28 \text{ Gm., wt. of both in water}\\
&\overline{29.77} \text{ Gm., buoyant effect of the cork}
\end{aligned}
$$

This value represents, not the total weight of water displaced by the cork, but only the weight necessary to force the cork from the floating position (where its weight would be zero) to complete immersion. Therefore, the total weight of water displaced would be obtained by adding to this value the weight of the cork in air, which is equal to the weight of water it displaced in the floating position.

$$29.77 + 9.40 = 39.17 \text{ Gm., wt. of an equal volume of water}$$

$$\frac{9.40 \text{ (wt. of the cork in air)}}{39.17 \text{ (wt. of an equal vol. of water)}} = 0.239, \text{ sp. gr. of the cork}$$

Special Method for Waxes.—A special method for determining the specific gravity for substances lighter than water, which may be applied when the substance is insoluble in hydroalcoholic mixtures, is the pharmacopoeial procedure,[1] which was official until Nov. 1, 1942, for determining the specific gravity of yellow wax and white wax. The principle involves the adjustment of the specific gravity of a mixture of alcohol and water to a point at which beads of the wax to be tested neither float nor sink in the liquid. Then by determining the specific gravity of the liquid the specific gravity of the wax is obtained. A similarity is noted between this method and the use of Lovi's beads in the determination of the specific gravity of liquids; but, in this case, the specific gravity of the liquid is adjusted to conform to that of the bead, and the object of the process is to find the specific gravity of the solid, rather than that of the liquid. The pharmacopoeial directions for the process are as follows:

"Melt the Wax at a low temperature, and allow it to fall in separated drops from just above the surface into alcohol that has been warmed to from 45° to 50°C. Allow the globules to remain in the alcohol until it has cooled spontaneously to room temperature (20° to 25°C.), then remove the Wax and keep it at room temperature for twenty-four hours. Prepare a mixture of four volumes of alcohol and enough distilled water to make ten volumes, and allow it to stand until free from air bubbles. Moisten the globules of Wax with distilled water by using a brush, and place them by means of forceps in the alcohol solution just prepared and contained in a beaker. Then add alcohol or air-free distilled water, as required, to the mixture, kept at 25°C., to make the globules of Wax float and rest indifferently in the liquid. Finally determine the specific gravity of the resultant alcohol-water mixture. The figure thus obtained represents the specific gravity of the Wax examined."

4. *Solids Heavier Than and Insoluble in Water (in Powdered Form).*—This class of solids differs only in physical form from the first class to be considered, namely, solids heavier than and insoluble in water. Examples of materials belonging to this classification are barium sulfate, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, bismuth subsalicylate, heavy magnesium oxide, mild mercurous chloride, precipitated calcium

[1] "The Pharmacopoeia of the United States of America," eleventh revision, p. 114.

carbonate, precipitated sulfur, purified siliceous earth, purified talc, reduced iron, sublimed sulfur, washed sulfur, yellow mercuric oxide, and zinc oxide. The fact that these substances occur in a more or less finely subdivided state makes hydrostatic weighings impossible. The usual procedure is to make use of a pycnometer for the purpose of determining, by difference, the weight of water actually displaced by a weighed quantity of the powdered substance. The following example illustrates the method of calculation:

A pycnometer, when completely filled with distilled water, weighs 42.50 Gm. When 10.00 Gm. of reduced iron is placed in the pycnometer and the remainder of the space is completely filled with distilled water, the total weight is 51.08 Gm. What is the specific gravity of the reduced iron?

Details of the method are suggested by the statement of the example. Three weighings are required, namely, (1) the weight of the reduced iron taken as a sample, (2) the weight of the pycnometer when completely filled with distilled water, and (3) the total weight of the pycnometer when it contains the weighed quantity of reduced iron together with a sufficient quantity of distilled water to occupy the remainder of the space. The calculation of the specific gravity of the reduced iron is made as follows:

42.50 Gm., wt. of pycnometer filled with water
10.00 Gm., wt. of reduced iron
52.50 Gm., theoretical wt., if no water were displaced
51.08 Gm., wt. of pycnometer, reduced iron and water
1.42 Gm., wt. of water displaced

Since the reduced iron has displaced 1.42 Gm. of water, this represents the weight of an equal volume of water. The specific gravity is obtained by dividing the weight of the reduced iron by the weight of an equal volume of water.

$$\frac{10.00}{1.42} = 7.042, \text{ sp. gr. of reduced iron}$$

It should be noted that the tared weight of the pycnometer does not come into consideration in this calculation, since the weight of the displaced water is determined by difference and not by direct weighing. It follows that the calculation could be made equally well by using net weights. As a practical suggestion, it is recommended that the weight of the sample should be determined by difference, after the tared weight of the pycnometer has been obtained, by placing approximately ten grams of the powder in the pycnometer and weighing accurately. This procedure eliminates the possibility of loss of the powder by transfer.

A frequent source of error in determining the specific gravity of powdered substances is the failure to remove completely the air bubbles that have a tendency to form within the bulk of the material. Many powdered substances, especially when in a fine state of subdivision, tend to repel water and do not become moistened immediately. As a result, air is occluded and held within the bulk of the powder, where it may escape detection. Gentle

shaking of the powder with a small amount of water in the pycnometer is sometimes helpful in overcoming this difficulty, or the air may be removed by carefully applying suction to the pycnometer. If the pycnometer has been filled to capacity, gentle tapping on the bottom of the pycnometer may dislodge the air bubbles. In more extreme cases, it may be necessary to allow the powder to stand in contact with the water for several hours before finally adjusting the volume in order to ensure the absence of air bubbles.

A less accurate method, which may be used when a pycnometer is not available, is to fill a cylindrical graduate to any convenient level sufficiently below its maximum capacity and then note the increase in volume when a weighed quantity of the powdered material is added. This increase in volume is the measure of the displacement caused by the powder. The weight of this volume of water is easily calculated and divided into the weight of the powder to obtain its specific gravity.

SPECIFIC VOLUME

Specific volume may be defined as the ratio of the volume of any substance to the volume of an equal weight of some other substance taken as a standard of comparison. In pharmacy, since we are especially concerned with the specific volume of solids and liquids, for which the standard of comparison is distilled water, the definition might be stated for our purposes as the ratio of the volume of a substance to the volume of an equal weight of distilled water. Mathematically, specific volume is the reciprocal of specific gravity and may be calculated directly from the latter by dividing specific gravity into 1.000, *i.e.*,

$$\text{Sp. vol.} = \frac{1.000}{\text{sp. gr.}}$$

Because of the reciprocal relationship, it follows that all substances having a specific gravity greater than 1.000 will have a specific volume proportionately less than 1.000, and vice versa.

An understanding of specific volume is necessary in order to interpret weight and volume relations. For example, many liquids are purchased by the pharmacist by weight and sold by volume units. In the compounding of a formula stated in terms of weight units, it is frequently more convenient to measure the volume of a liquid that is equivalent to a given weight. This volume may easily be calculated from the specific volume of the liquid.

A liquid that is purchased by the pound (av.) but that frequently is sold by the pint or fluidounce is glycerin, which has a specific gravity of approximately 1.250. Accordingly, its specific volume would be 1/1.250, or 0.800. If we wish to determine the volume, in units of the U.S. fluid system, for 1 lb of glycerin the calculation would be as follows:

Since 1 f ℥ of distilled water weighs 454.6 gr. at 25°C., 1 lb. (7,000 gr.) of distilled water would contain 7,000/454.6, or 15.398 fluidounces. But 1 lb. of glycerin, which has a specific volume of 0.800, would occupy only 0.800 as much space.

Therefore, 15.398 × 0.800 = 12.3184 f℥, or approximately 12 f℥, 2 f℥, and 32⅘ ℥.

The conversion is even simpler in the metric system. While theoretically 1 cc. of water weighs 1 Gm. only at 4°C., it is customary, in practical applications, to neglect the slight error introduced by assuming that the values are equivalent at ordinary room temperature. If we wish to calculate the volume of 500 Gm. of glycerin, the calculation would be as follows:

$$500 \times 0.800 = 400 \text{ cc.}$$

If, in the applications of specific gravity and specific volume to weight and volume units expressed in the metric system, the slight error due to difference in temperature is ignored, the relationships that follow may be stated; they will be found useful in making conversions.

Wt. in Gm. × sp. vol. = vol. in cc.
Wt. in Gm. ÷ sp. gr. = vol. in cc.
Vol. in cc. × sp. gr. = wt. in Gm.
Vol. in cc. ÷ sp. vol. = wt. in Gm.

VISCOSITY

Another characteristic property of fluids (both liquids and gases) is viscosity. In pharmacy we are particularly concerned with its application to liquids. In general, the viscosity of a liquid is the resistance that it offers upon being poured from one container to another, or in conforming to the shape of the container in which it is placed. In other words, it is a manifestation of the forces that arise within a liquid in opposition to flow and is therefore a measure of the combined effects of adhesion and cohesion.

A liquid that flows easily is said to have a low degree of viscosity and a correspondingly high degree of mobility or fluidity. Examples of mobile liquids are alcohol, water, ether, and chloroform. Syrups, heavy oils, clarified honey, and some of the mucilages are examples of viscous liquids.

The viscosity of a liquid is influenced by a number of factors, such as the density of the liquid in question, the temperature at which the determination is made, and, since most determinations are based upon the rate of flow of the liquid through a tube, the force with which the liquid is propelled. In its passage through a tube all parts of a liquid do not move at the same velocity because of the attraction of the surface for the tube and the internal friction of the molecules of the liquid. Thus, the flow of the

liquid involves the movements of a series of tubes, passing one over the other at different velocities, in a manner similar to the movements produced in the various sections of a telescope as the instrument is extended. It has been found, by careful measurement, that the force per unit area necessary to maintain the condition of flow is directly proportional to the velocity of the adjacent layers of liquid and inversely proportional to the distance separating these layers. The coefficient of viscosity, which Webster's Dictionary defines as "The ratio of the tangential frictional force per unit area to the gradient of velocity perpendicular to the direction of flow of a fluid," is based upon these principles.

Viscosity may be expressed by a number of terms; hence the terms **relative viscosity, absolute viscosity,** and **kinematic viscosity.** The methods for determining viscosity vary considerably, depending on the type of liquid to be tested and the style of instrument, called a viscosimeter, that is employed. The usual method is based upon a measurement of the time of flow for a measured quantity of liquid through a calibrated tube. Other variations include the rotating cylinder type of instrument, in which the frictional force necessary to revolve a cylinder within the liquid is measured, or the float type of instrument, designed especially for testing extremely viscous liquids such as asphalt.

Relative Viscosity.—As the term implies, relative viscosity is the ratio of the time of outflow of a measured quantity of the liquid as compared with the time of outflow for the same quantity of distilled water measured in the same instrument at the same temperature. This form of viscosity was recognized by the ninth revision of the Pharmacopoeia, and specific directions for determining it are found in the monograph on Petrolatum Liquidum. The directions for the determinations are as follows:

Make a permanent mark about 2 cm. below the bulb of a 50 mil pipette of the usual type and note the time, in seconds, required at 25°C. for the level of distilled water to fall from the upper to the lower mark as the liquid flows from the pipette. The time should not be less than twenty-five seconds nor more than thirty seconds for the pipette selected.

Draw the Liquid Petrolatum to be tested into this pipette, which should be clean and dry, and note the time, in seconds, required at 25°C. for its level to fall from the same upper to the lower mark as used for

the water. Divide the number of seconds thus noted by the number of seconds required for water to fall from the upper to the lower mark, as above determined. The quotient indicates the viscosity. Distilled water at 25°C. is taken as 1.

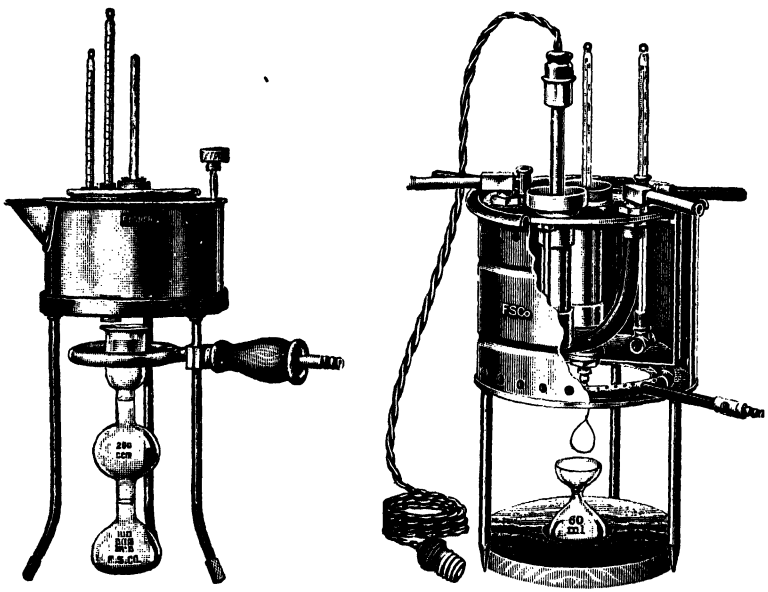
Absolute Viscosity.—In general terms, absolute viscosity may be defined as the force that will move a unit area of plane surface of a liquid, with unit speed relative to another parallel plain surface, from which it is separated by a layer of the liquid of unit thickness. The unit of absolute viscosity that is commonly used is called the **poise,** which is equivalent to the force of one dyne-second per square centimeter. The dyne is a unit of force of such magnitude that a particle whose mass is 1 Gm. would, under its influence, undergo an acceleration in velocity of 1 cm. per sec.

Kinematic Viscosity.—The official form for expressing viscosity adopted by the Pharmacopoeia is kinematic viscosity, which is briefly discussed in a pharmacopoeial monograph.[1] Kinematic viscosity may be defined as the ratio of absolute viscosity when expressed in poises (or centipoises) to the density of the liquid. The units that are more properly used with reference to kinematic viscosity are the **stoke** and **centistoke.** The value of the stoke is that of a fluid which has an absolute viscosity of 1 poise and a density of 1 Gm. per cc. Thus, for distilled water, it can be seen that the stoke is approximately equivalent to the poise. This relationship does not hold true for other liquids but varies according to the density of the liquid.

Since both absolute and kinematic viscosity are difficult to determine directly, it is customary to use such instruments as the Saybolt Universal, the Saybolt Furol, the Engler, the Redwood I, and the Redwood II viscosimeters. The Saybolt instruments are the most widely used in the United States, the Engler instrument is more commonly used in Germany, and the Redwood viscosimeters find greater use in England. The Redwood II and the Saybolt Furol viscosimeters are intended for extremely viscous liquids, being provided with wider capillaries than those of the other instruments. The time of outflow obtained with the Saybolt Furol instrument usually approximates one-tenth the value obtained on the same liquid at the same temperature with the Saybolt Universal viscosimeter. Readings

[1] *Ibid.*, twelfth revision, p. 633.

for both the Redwood and the Saybolt instruments are expressed as the number of seconds of time required for the outflow of a standard volume of liquid. The readings obtained with the Engler instrument are usually expressed in terms of Engler degrees; however, these values are obtained by dividing the efflux time in seconds for the liquid by the efflux time in seconds for an equal volume of distilled water at the same temperature.



Engler. Saybolt universal.

FIG. 37.—Viscosimeters.

The official monograph on kinematic viscosity contains a table[1] that may be used for converting kinematic viscosity, expressed in centistokes, into the corresponding Saybolt Universal readings, or vice versa. The table shows equivalent values for kinematic viscosities extending from 2 to 70 centistokes and lists the corresponding Saybolt Universal readings (time of outflow in seconds) in three columns that correspond to the appropriate values at 37.8°C. (100°F.), 54.4°C. (130°F.), and 98.9°C. (210°F.). Kinematic viscosity is specifically required as

[1] *Ibid.*, p. 634.

a basis for identification of Petrolatum Liquidum and Petrolatum Liquidum Leve.[1]

REFRACTION

Another physical property of certain substances of considerable importance in its application to liquids is known as refraction. This phenomenon is based upon the behavior of light when passing obliquely from one medium into another of different optical density as, for example, from air into water. In general, the term *refraction* applies not only to light rays, but to heat and sound waves as well, and indicates the deviation from a straight path that the rays undergo. In considering the refraction of light, it must necessarily follow that measurements are possible only in the case of transparent substances; it should also be noted that no deviation occurs if the direction of propagation is perpendicular to the surface of the denser medium. Refraction occurs only if the ray of light strikes the surface of the denser medium at an oblique angle.

From a theoretical point of view, the **absolute index of refraction** may be defined either as the ratio of the velocity of light in a vacuum (or, for ordinary working conditions, in air) to that in a given medium or as the ratio of the velocities of light in two different media.

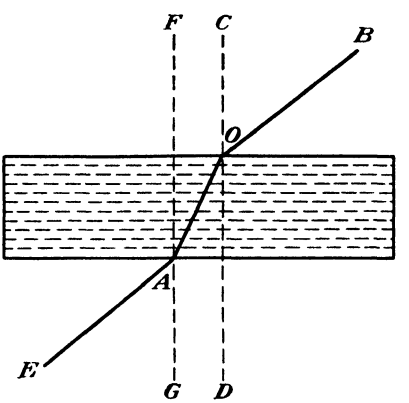


FIG. 38.—Refractive index.

Index of Refraction.—According to Snell's law, the index of refraction is defined as the ratio of the sine of the angle of incidence to the sine of the angle of refraction that is observed when light passes obliquely into a medium of different optical density. The explanation of this definition may be more readily followed by reference to Fig. 38, which illustrates the path of a ray of light in passing from air, a rare medium, into water, which is a denser medium. Both the angle of incidence and the

[1] *Ibid.*, pp. 353–354.

angle of refraction are measured with reference to the perpendicular. Thus, the angle of incidence in this figure is the angle *BOC*, and the angle of refraction is the angle *AOD*.

The term **sine** is the name of a trigonometric function that deals with the measurement of angles in a right-angled triangle. Specifically, it is the ratio of the length of the side opposite the given angle to the length of the hypotenuse of the triangle. Repeated experiments have demonstrated that for a given substance, when tested with the same kind of light, the ratio of the angles of incidence and refraction, as well as the ratio of the sines of these angles, remains constant, regardless of the value of the angle of incidence. This constant ratio is known as the index of refraction. It may be expressed algebraically as follows:

Let I = the angle of incidence
R = the angle of refraction
and n = the index of refraction,

Then

$$n = \frac{\sin I}{\sin R}$$

or

$$\sin R = \frac{\sin I}{n}$$

and

$$\sin I = n \sin R$$

In passing from the denser to the less dense medium, as shown at A in the figure, the light ray undergoes refraction according to the law that governed its behavior upon entering, but in the reverse direction. Accordingly, the angle EAG is equal to the angle BOC, and the angle OAF is equal to the angle AOD. Hence, if the lower surface of the medium is parallel to the upper surface, the emergent ray AE will be parallel to the entering ray BO.

Since the refractive index is a physical property, it may be used in much the same way as the specific gravity, boiling point, or melting point of a substance as a confirmatory test for its identity or as a means of detecting adulteration. The fact that the determination is dependent upon the transmission of light tends to restrict its application, for the most part, to transparent liquids. The Pharmacopoeia and the National Formulary list

the refractive indices for the volatile oils and other liquids. Additional information on the fixed oils, organic solvents, and other unofficial liquid substances may be found in chemical handbooks and other references. Frequently the abbreviation used to indicate the refractive index may appear as $n_D^{20^\circ}$ or $n_D^{25^\circ}$. The figures indicate the temperature (in degrees centigrade) at which the reading was made, and the letter *D* signifies that the determination was made by using light rays corresponding to the *D* rays of the spectrum (the light emitted by incandescent sodium). Although determinations of refractive index are usually not included in a beginning laboratory course in pharmacy but are reserved for later consideration, brief mention of this property is given at this point in order that the term may be understood whenever it is encountered in the study of official substances.

Specific and Molecular Refractivity.—Although the refractive index of a substance varies with temperature, Gladstone and Dale[1] found that the expression $(n - 1)/d$, in which d represents the density of the substance, remains nearly constant at different temperatures. The same holds true to a still greater extent if the formula as developed by Lorentz and Lorenz[2] is used. Their formula is as follows:

$$\frac{n^2 - 1}{n^2 + 2} \times \frac{1}{d} = k$$

in which n is the index of refraction of a liquid at a given temperature, d is the density of the substance at the same temperature, and k is a constant known as the **specific refraction.** This value is nearly independent of the temperature at which the readings are made. The product $M \times k$, where M is the molecular weight of the substance, is the **molecular refraction,** which represents a value characteristic of, and peculiar to, a given substance in the same way as do the other physical properties under discussion in this chapter.

Refractometers.—The instruments used to determine the refractive index are known as refractometers. These vary considerably in the details of their construction and in their use, but all are based on the same principle, which involves measuring the deviation of a ray of light when it is passed through a layer or film of the substance being tested at an oblique angle. The most

[1] A. FINDLAY. "Practical Physical Chemistry," Longmans, Green and Company, New York, 3d ed., 1920, p. 98.

[2] S. SMILES. "The Relation between Chemical Constitution and Some Physical Properties," Longmans, Green and Company, New York, 1910.

common types of refractometer are the Abbe and the dipping, or immersion, refractometers.

The Abbe Refractometer.—This name is applied to a type of instrument, rather than to one produced by a specific manufacturer, for several manufacturers of optical instruments have designed instruments of the same general class. The essential parts consist of (1) the double Abbe prism, made of highly refractive glass, which holds the film of liquid to be tested between the two prisms and which can be rotated on a horizontal axis, the position of the prism being indicated by the movement of an arm over a graduated sector; (2) a telescope for observing the border line of total refraction; (3) a compensator, which serves to correct for chromatic aberration, converting the border line of total refraction into a colorless line; and (4) a sector, which is rigidly attached to the telescope, graduated in terms of refractive indices, and usually extending from 1.300 to 1.700. The prisms are provided with water jackets through which water at an accurately controlled temperature is circulated for some time prior to and during the taking of readings.

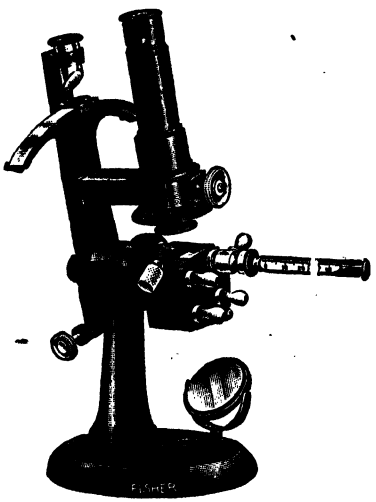


FIG. 39.—The Abbe refractometer.

The Dipping Refractometer.—This instrument is designed to cover a smaller index range than the Abbe type of instrument, but with a higher degree of accuracy. In general, it is used for those liquids having indices of refraction ranging from 1.325 to 1.366. If higher ranges are desired, special prisms may be added, but these must be incorporated in the optical system at the factory and are not demountable. The dipping refractometer is used in conjunction with a special refractometer bath equipped with a glass plate in the bottom and a mirror to reflect light up through the samples. The bath is filled with water of known temperature, and the samples of liquid to be tested are placed in small beakers

on a special inclined shelf, so arranged that the beakers are partly immersed in the water. The prism of the refractometer is then dipped into the sample to be tested. After correcting for chromatic aberration by appropriate adjustment of the compensator, the position of the line of total refraction is noted with reference to an arbitrary scale, which is found in the field of the instrument, extending from 0 to 100. Conversion to refractive index is

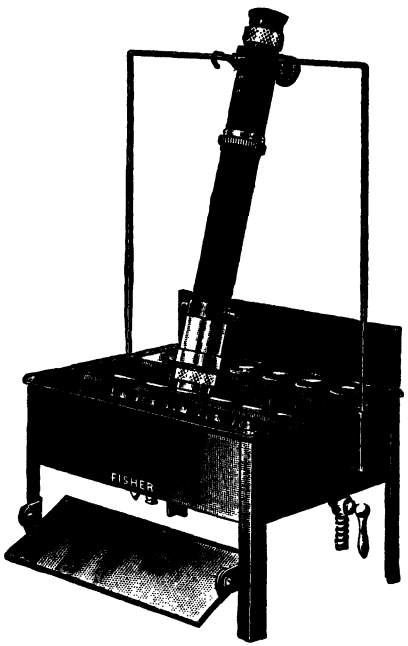


FIG. 40.—Dipping refractometer.

usually made by reference to a table furnished with the instrument, or the value may be derived mathematically. The greater degree of accuracy that may be obtained with this instrument is due to the fact that a narrower range is covered, which permits a greater degree of magnification of the border line, with a resulting increase in the sharpness of the image.

Fisher Refractometer.—A relatively new type of refractometer, which employs the principles reported by Dr. E. E. Jelley, has recently been made available. This instrument permits direct reading of the refractive index on an illuminated, transparent

scale and covers a range of 1.30 to 1.90, with subdivisions of 0.01. Extremely small quantities of liquids may be tested with this instrument, the sample being placed in a small wedge-shaped well located at the eyepiece. Light is admitted at a slit at the front of the instrument, and the virtual image of the slit is projected onto the illuminated scale. The instrument has no moving parts and is much less expensive than either of the two instruments described in the preceding pages.

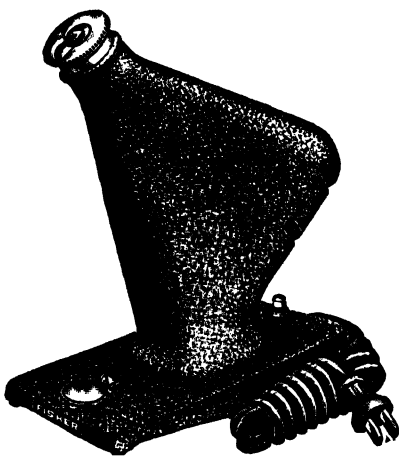


FIG. 41.—Fisher refractometer.

OPTICAL ROTATION

Another physical property of considerable importance, particularly in its application to certain types of organic compounds, is known as **optical rotation.** This phenomenon is based upon the use of plane-polarized light, commonly called polarized light. The earlier view of the transmission of light, which succeeded the corpuscular theory as advocated by Newton, was known as the wave theory. According to this, it was assumed that light is a longitudinal form of wave motion similar to that of sound waves except that the waves are of higher frequency and shorter in length. It was not until the study of the phenomenon of polarization in 1808 that physicists were forced to adopt the transverse-vibration theory of light. According to this theory, the vibrations in a ray of ordinary light occur in a plane at right

angles to the direction of propagation, with the direction of vibration constantly changing. In a ray of polarized light, the vibrations are also transverse but take place in only one direction.

As early as 1669, it was observed that, when light passes through a prism of Iceland spar (calcite), it is transmitted as two distinct beams. This phenomenon is known as double refraction. One ray of light is found to be completely refracted, following the direction indicated by Snell's law of refraction. This ray was called the ordinary ray. The other ray passed through the prism and was called the extraordinary ray. Further investigation revealed that the extraordinary ray consisted of vibrations in only a single plane. An application of this principle has been made in the Nicol prism, which is named for its inventor. This device furnishes a convenient means for generating plane-polarized light. It is produced by cutting a crystal of Iceland spar along its optical axis, carefully removing a wedge-shaped segment, and cementing the polished cut surfaces together with Canada balsam. This is done in such a way that the ordinary ray is totally refracted and only the extraordinary ray passes through the prism. Although the ray that emerges possesses less than half the intensity of the entering ray, it is plane-polarized, or consists of vibrations in a single plane.

When plane-polarized light is passed through certain substances, especially liquids and solutions of solid substances, the plane of these vibrations is twisted, or rotated, to either the right or the left, depending upon the nature of the substance. Such a substance is said to be optically active or to possess the property of optical rotation. It is customary to refer to the activity as **dextrorotatory** (dextrogyrate) if the direction of rotation is to the right and **levorotatory** (levogyrate) if the rotation is to the left.

Although optical rotation may, in some cases, be a property of certain naturally occurring mineral substances and may also be induced by passing polarized light through certain substances in the presence of a magnetic field, we are primarily concerned with optical rotation which is due to a peculiarity in the molecular structure of certain organic compounds. The optical activity of these compounds is attributed to the presence of one or more asymmetric carbon atoms within the molecular structure of these

substances. An asymmetric carbon atom may be defined as one connected with four groups, no two of which are alike in structure. Among the common examples of organic compounds that are optically active because of this peculiarity of structure are the naturally occurring sugars, such as sucrose, maltose, lactose, dextrose, and fructose.

In order to measure the rotatory power of optically active substances, special instruments have been devised which are known as polarimeters, polariscopes, or, when used especially for the determination of sugars, saccharimeters. The polarized light must be transmitted through a substance in order to measure its optical activity. For this reason, solutions of solid substances (in optically inactive solvents) are prepared for examination in the instrument. Since the optical rotation is directly proportional to the concentration and the length of the column of solution (or liquid) being tested, it is necessary to limit these factors in order that comparisons may be made.

Specific Optical Rotation.—In addition to the influence of the concentration and the length of the column of liquid tested upon the reading, it has been found that the results may also be affected by the temperature and the kind of light employed. The standard value for comparison of the power of optical rotation is called the **specific optical rotation,** which is commonly designated by the symbol $[\alpha]_D^t$. This may be defined as the number of angular degrees of rotation produced when a solution corresponding to a concentration of 100 Gm. in 100 cc. is examined in a tube 1 dm. long, in monochromatic light corresponding to the D rays of the spectrum (sodium light), at the temperature indicated by the letter *t* in the symbol. By international agreement, 20°C. has been adopted as the standard temperature at which saccharimeter readings are made, and this is likewise the temperature most frequently found in tabulations of specific optical rotations in reference books and handbooks. Consequently, the symbol for specific optical rotation usually appears as $[\alpha]_D^{20}$. Since optically active substances may be either dextrorotatory or levorotatory, it is customary to use a plus sign [+] before the reading to indicate a reading to the right and a minus sign [−] before the number of degrees to indicate a reading to the left.

Since the specific optical rotations of many organic compounds are known, the polariscope affords a rapid and convenient method for the quantitative analysis of such substances. By computing the theoretical specific optical rotation from the observed reading of a sample of unknown strength and comparing this with the known specific optical rotation of the pure substance, its percentage composition may readily be obtained.

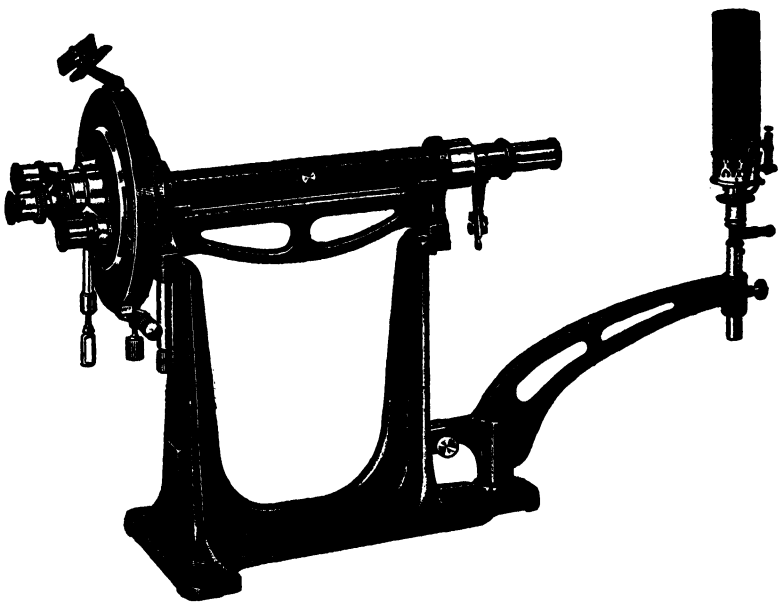


FIG. 42.—The polarimeter.

The Polarimeter.—The instruments used for measuring the extent of optical activity are the **polarimeter** (or polariscope) and the **saccharimeter.** The polarimeter is calibrated in angular degrees and consists essentially of a polarizer and an analyzer, both of which are Nicol prisms that are separated so that the optically active substance, contained in a polariscopic tube fitted with transparent windows at either end, may be interposed. The polarizer remains in fixed position, but the analyzer may be rotated to compensate for the rotation of the substance being tested. The movement of the analyzer is registered in angular degrees and minutes. Details of the end-point device may vary, some instruments employing the triple-shadow and others the half-shadow device. The appearance of the field for each of these types of end-point devices when in a position such that the prisms are crossed, *i.e.*, when the analyzer is not in the same plane as the rays transmitted by the polarizer, is shown in Fig. 43. In effect, the end point of the

instrument is reached by turning the analyzer until all parts of the field of vision are equally illuminated.

The Saccharimeter.—A modification of the polarimeter intended for the special purpose of determining sugars is known as the saccharimeter. Instead of being calibrated in angular degrees, these instruments employ arbitrary degrees, either of the Ventzke sugar scale or the Laurent (French)

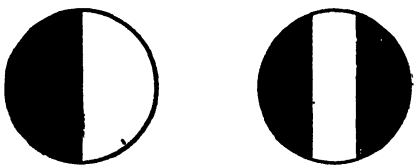


FIG. 43.—Polarimeter end-point devices.

sugar scale. The values of these units are selected in such a way that, when a predetermined weight, sometimes called the "normal weight," of a sugar sample (which varies for each sugar, since it is based upon the specific optical rotation of that particular sugar) is dissolved in sufficient water to prepare 100 cc. of solution and this solution is examined in a 200-mm. tube, the reading, in terms of the degrees of the scale being used, will correspond to the percentage of that particular sugar in the sample. For converting

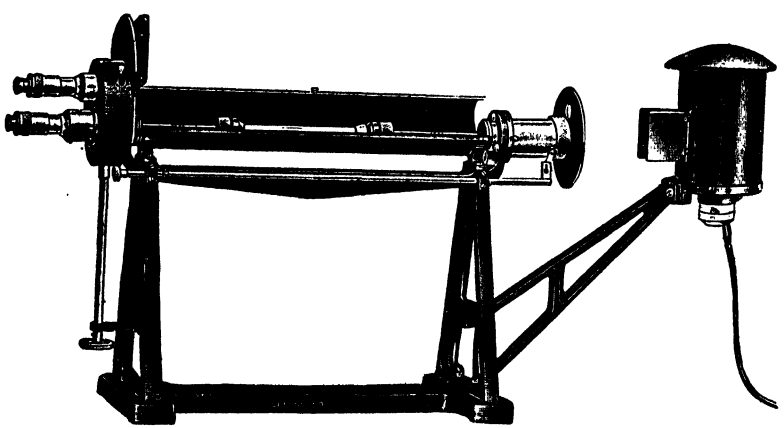


FIG. 44.—The saccharimeter.

readings of the saccharimeter into angular degree readings, the following factors are used:

1 deg. Ventzke equals 0.3468 deg. angular rotation.

1 deg. Laurent equals 0.2167 deg. angular rotation.

The Ventzke scale is used by the Schmidt and Hänsch, the Peters, and the Fric saccharimeters. The Laurent scale is found on the Laurent-Jobin and the Duboscq-Pellin saccharimeters.

COLORIMETRY

When light passes through a solution of a colored substance, some of it is absorbed. The higher the concentration of the substance responsible for the color, the greater will be the absorption of light. Thus the measurement of the amount of absorption serves as a means of determining the concentration of the colored constituent. This method is known as **colorimetric analysis** or **colorimetry,** and the instruments used for this purpose are known as **colorimeters, color comparators,** or **tintometers.** Such determinations are usually based upon a direct comparison with a standard solution (a solution of known concentration) of the substance under investigation. This may be done in three ways, (1) by varying the amount of the chemical substance in a given volume of solution until it matches the color of the unknown solution, (2) by dilution of the solution of a given weight of the colored substance until it matches the color of the unknown solution, and (3) by matching the color of the two solutions by changing the thickness of the column through which the light must pass for one of the solutions, the thickness of the column of the other solution remaining constant.

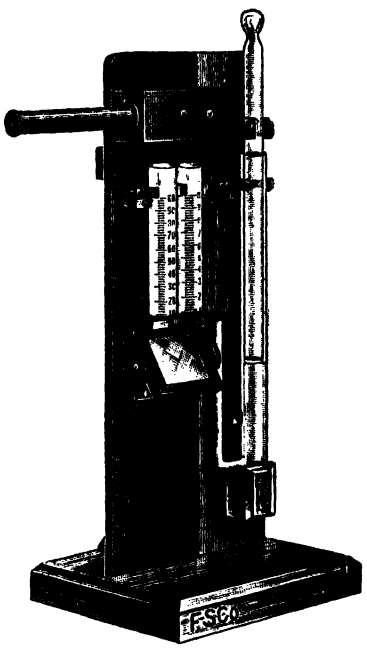


FIG. 45.—Colorimeter.

Although fairly accurate comparisons may be made directly by simply viewing the two liquids (contained in tubes of like dimensions and of the same grade of glass) transversely against a white background, the determination is more conveniently made by using an instrument especially designed for this purpose. The principle usually applied is that of varying the thickness of the column of one of the solutions, either by changing the position

of a piston in a cylinder containing a reserve supply of the liquid or by raising or lowering the level of a plunger (a glass prism through which the light passes) by means of a rack-and-pinion device. In either case, the color imparted to the light that passes through the two liquids is transmitted by means of reflectors onto the two halves of the circular field, which is viewed through the eyepiece. When the two halves of the field show no perceptible difference in color, the liquids are considered matched, and the relative concentrations may be calculated by comparing

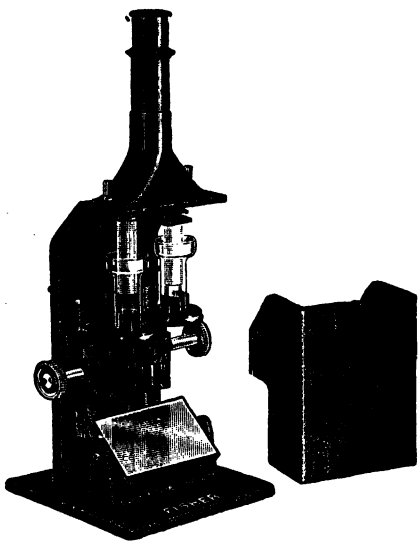


FIG. 46.—Duboscq colorimeter.

the relative heights of the two columns; the concentration of a given solution varies inversely with the height of column necessary to match the two liquids. Some of the instruments of the Duboscq type are provided with reading scales, which may be read directly from the eyepiece position.

The Electrophotometer.—Within recent years the application of the electrophotometer to colorimetric determinations has been introduced. Although it is beyond the scope of this book to discuss in detail this instrument and the principles upon which its operation is based, it is being mentioned at this point in order that it may be known that such instruments are available. They

represent a particularly useful tool in many colorimetric determinations, especially in the field of biochemistry and in manufacturing pharmacy. Because of its greater sensitivity, the instrument is capable of detecting differences in color that are indiscernible to the eye. A potentiometer is employed in this instrument to measure the current output of a photoelectric cell, the output being directly proportional to the amount of light

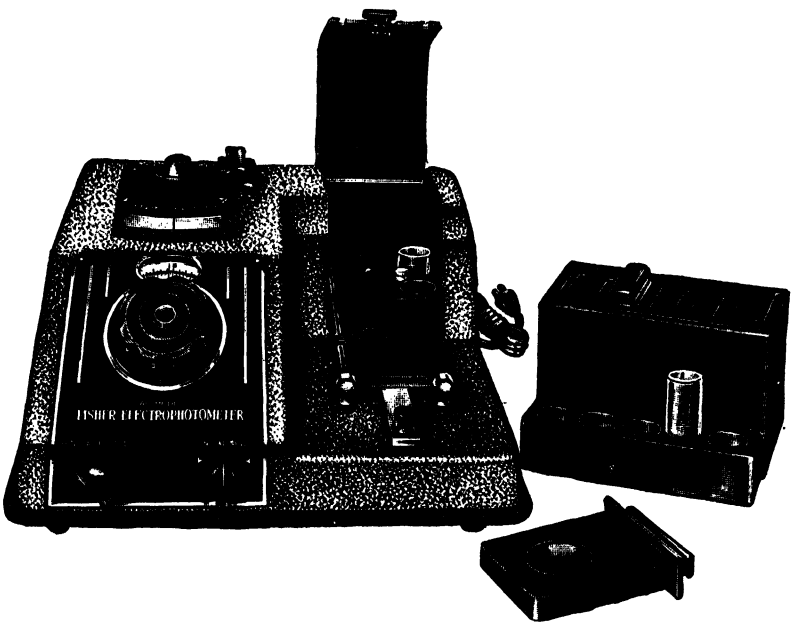


FIG. 47.—The electrophotometer.

that strikes the surface of the cell. The light that is transmitted through the colored solution is directed to the photoelectric cell, and the reading is taken from the scale of the potentiometer. By comparison of this value with that obtained with a standard solution, either directly or by referring to a plotted curve as circumstances may require, the concentration of the unknown solution may readily be determined.

SURFACE TENSION

A physical property of considerable importance in its influence on the behavior of liquids is known as **surface tension.** This

may be defined as that property arising from molecular forces which manifests itself in the tendency of the surface film of all liquids to bring the contained volume into that form having the smallest possible superficial area. It will be recalled that the ratio of surface to volume is less in the sphere than in any other conformation. The tendency of a falling drop of a liquid to form an almost perfect sphere is the result of surface tension, as is the spherical form of soap bubbles. This effect is utilized in a practical way in the manufacture of lead shot by permitting molten lead to pass through a sieve and fall through a shot tower into a pool of water. The familiar experiment of the greased needle that is floated on water, despite the fact that the needle has a greater specific gravity, is an example of the effect of surface tension, as is the apparent ability of certain insects to walk on the surface of water. Although it presents a purely hypothetical view that is out of harmony with the facts in the case, it is nevertheless helpful in gaining an understanding of surface tension to consider the film on the surface of a liquid as a stretched elastic membrane that tends to contract whenever possible. Many of the effects which are produced by surface tension are comparable to those which would be brought about by such an elastic membrane.

The explanation of surface tension depends on an understanding of cohesion. The latter may be described as an attractive force that like particles or molecules exert mutually upon each other. If we consider the effect of cohesion on an individual molecule, located well beneath the surface of a liquid, we find that it is attracted to the molecules surrounding it; but these forces offset each other, since they extend in all directions in space, so that molecular equilibrium is maintained. Now consider another molecule, located at the surface of the liquid. The molecular attraction here tends to pull the molecule downward, and there is no compensating force tending to pull the molecule upward. The result is that the molecules in or adjacent to the surface are pulled toward the interior of the liquid, and this force tends to decrease the surface of the liquid.

Cohesion and Adhesion.—The explanation just given for surface tension indicates that it is the result of attraction of like particles or molecules. This force is known as **cohesion.** At

the same time, attractive forces may exist between molecules or particles that are unlike each other, as between wood and glue or between stone and cement. This kind of attraction is known as **adhesion.**

Capillarity.—The term *capillarity* is used to indicate the action by which the surface of a liquid, where it is in contact with a solid (as in a capillary tube), is elevated or depressed. Capillary attraction depends on the relation between the attraction of the molecules of the liquid for each other (cohesion) and their attrac-

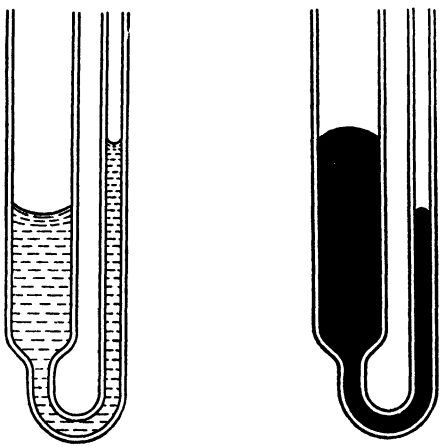


FIG. 48.—Capillary effect of water and mercury in small tubes (*From N. H. Black, "An Introductory Course in College Physics," The Macmillan Company, New York,* 1935.)

tion for the molecules of the solid (adhesion). The effect of capillarity is easily demonstrated by observing the level that liquids attain in tubes of small diameter (called capillary tubes, from *capillus,* a hair, because hairlike dimensions are approximated). The capillarity of the liquid determines the extent of the increase or decrease above or below the general level of the liquid, which is shown when one end of the tube is dipped in the liquid.

Assume that we have two U tubes (Fig. 48) with their side tubes having diameters of 30 mm. and 1 mm., respectively. If one tube is filled with water and the other with mercury, it will be observed that, in the case of each liquid, the levels in the two

arms of the tube are unequal, which is not in accord with the general law of hydrostatics that a liquid will stand at the same level in two communicating vessels. This abnormality is due to capillarity, and the difference in the behavior of the two liquids may also be explained. The water wets the surface of the glass and is attracted by it, which means that the adhesion is great. On the other hand, the mercury does not wet the glass because the force of adhesion is less than the force of cohesion of the particles of mercury to one another. This gives the appearance of a repulsion between the glass and mercury. It will be noted that the surface of the mercury is convex, while that of the water is concave. In the case of the water, each tube tends to draw up the liquid against the force of gravity; and, the narrower the tube, the higher the water is raised.

This antagonism between the forces of cohesion and adhesion, or the capillarity of the liquid, explains why the surface of liquids in narrow containers appears, not as a horizontal plane, but as a curved surface, the degree of curvature tending to increase as the diameter of the tube decreases. The curved surface of the liquid is known as a *meniscus* (plural, *menisci*). When measurements of the volume of liquids are made in a wider container, this effect is not pronounced; but, in such devices as narrow cylindrical graduates, pipettes, and burettes, care must be taken to avoid error in reading because of the curved surface of the meniscus. Most liquids are attracted to glass or are said to have the ability to wet glass. (Mercury is an outstanding exception.) These liquids, therefore, have concave menisci. The rule that is always followed is to use the lowest point of the meniscus as the point of reference. However, since this point is in the center of the pipette, burette, or other measuring device, error will be introduced unless the meniscus is held at the level of the eye. If it is held above eye level, the angle of the line of sight will be such as to give a value in excess of the true volume; if held below, the reading will be less than the true volume. This source of error is sometimes spoken of as the effect of **parallax.**

Many instances may be found in which the surfaces of liquids, when in contact with solids, assume shapes and positions which are apparently at variance with the laws of hydrostatics; such cases are considered as examples of capillarity. A few of the

familiar illustrations include the soaking up of water by a sponge, the penetration of varnish into wood, the rising of oil in the wick of a lamp, the clinging of ink to a pen point, the flow of ink from pen to paper, the absorption of ink by blotting paper, the travel of moisture through the soil, and the permeation of a powdered drug by the menstruum in percolation and other processes of extraction.

The Measurement of Surface Tension.—The value of the surface tension may be determined in several ways, as by **the determination of the height to which the liquid rises in a capillary tube,** or by the **drop method,** in which an instrument known as the **stalagmometer** is used to determine the number of drops obtained from a measured volume of the liquid that is made to drip from a tube of known diameter, or by **direct measurement** by means of an instrument known as the **tensiometer.**

For the purpose of explaining how surface tension is evaluated, the capillary-tube method will be discussed briefly. This method of determination is based upon a measurement of the height to which a liquid rises in a capillary tube of known diameter. Let us assume that water rises to a height h in a tube which has the radius of its bore represented by r. The surface tension on each linear centimeter of surface is represented by the symbol T, which is expressed in terms of **dynes.** The dyne is a very small unit of force, which approximates a value of about one milligram. More accurately, 980 dynes is equal to 1 Gm. It should perhaps be explained that the value 980 is based upon the acceleration due to gravity, which is equivalent to 32 ft. per sec.^{2}, or 980 cm. per sec.^{2} The value for T will of course vary for different liquids, and for the same liquid at different temperatures.

For the purpose of explanation, the film on the surface of the water may be regarded as a membrane stretched tightly in all directions. If a slit 1 cm. long were to be cut in this membrane, a force of T dynes would be acting on each side of the slit, tending to pull it open. But the surface tension is acting around the edge of the top of the column contained in the capillary tube, which represents a distance of $2\pi r$, and therefore the total upward force amounts to $2\pi rT$ dynes. It is this force which holds the column of liquid in the tube above the general level of the liquid. The weight of the column may be computed, if d is the density

of the liquid in grams per cubic centimeter, as πr^2hd. This weight, expressed as πr^2hdg dynes, in which g is the acceleration due to gravity, is equal to the upward force due to surface tension. Therefore,

$$2\pi rT = \pi r^2hdg$$
$$T = \tfrac{1}{2}rhdg$$

or

$$h = \frac{2T}{rdg}$$

This indicates that the height of the capillary column is inversely proportional to the radius (and the diameter) of the tube. The

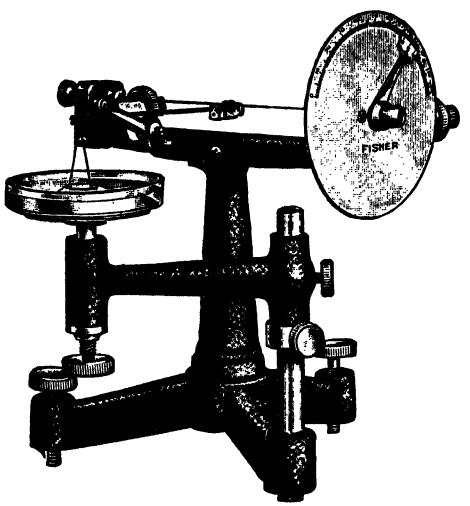


FIG. 49.—Surface tensiometer.

value for T for water at 25°C. is about 72 dynes per centimeter; at 100°C., it is about 59 dynes per centimeter. The approximate values for a few of the common solvents, expressed in terms of dynes per centimeter at 20°C., are as follows: acetone, 24; alcohol, 22; benzene, 29; chloroform, 27; ether, 17; glycerin, 63.

The Tensiometer.—A more convenient method for the determination of surface tension is by means of an instrument especially designed for the purpose, which is known as the tensiometer. The type of instrument, shown in Fig. 49, is known as the Cenco-du Nouy precision-form surface tensiometer.

As can be seen from the figure, the instrument is essentially a delicate torsion balance, which applies a slowly increasing upward force to a platinum-iridium ring in contact with the surface of the liquid to be tested. The amount of upward force is indicated by a circular graduated scale, which, upon being calibrated, gives readings directly in terms of dynes of force. The instrument is provided with a long torsion wire, secured at both ends by torsion heads driven by worm-gear arrangements, which permit very accurate adjustments. The side arm supporting the platinum-iridium ring is clamped in position at the middle of the torsion wire. It is claimed that readings may be made with this instrument which may be reproduced within a variation of ± 0.05 dyne.

Applications of Surface and Interfacial Tensions.—In addition to the surface tensiometer, a special instrument has been developed that employs the same principle for the measurement of the interfacial tension at the zone of contact of two immiscible liquids. The applications of surface tension and interfacial tension data to industrial processes are many and varied in character. Within recent years, the influence of these properties upon the behavior of liquids has become well recognized, and new methods and processes of manufacture and control are rapidly being developed, which are the outgrowth of further study and investigation in this special field of physical measurements. The properties of liquids with regard to surface tension or interfacial tension are involved in the phenomena of adsorption, cataphoresis, osmotic pressure, condensation, emulsification, evaporation, miscibility, and solubility. Industries dealing with dye solutions, the clarification of liquids, the flotation process in the refinement of ores, and many other processes may attain a higher degree of uniformity in their products and greater efficiency in manufacture by proper control of the surface tension of the processing liquids. It has recently been shown that a close relationship exists between the interfacial tension of oil-liquid systems and the lubricating value of oils as determined by standard lubrication testers.

Wetting Agents.—One of the outstanding developments of industrial chemistry within the past decade has been the production and utilization of a class of products that are commonly

called wetting agents, emulsifying agents, detergents, suspending agents, or penetrating agents. Although not a single class of substances but a constantly increasing list representing many types of organic compound, they are all spoken of as being surface active. That is, they have the capacity of modifying the surface tension and the interfacial tension of the liquid or liquids with which they are used, and it is this property which renders them useful in many manufacturing processes. A few of the industries that are using products of this nature in ever-increasing quantities include the textile, the leather and tanning, paint and varnish, and insecticide and fungicide industries, metallurgy, the food industry, rubber manufacture, and the printing-ink industry. Despite the fact that the commercial production of these items has developed since about 1929, the annual production in the United States for 1941 reached the total of 100,000,000 lb.,[1] and their use is increasing.

Although a few of the substances that are now used because of their properties as surface-active agents have been known for a long time, they were not utilized for such purposes until recently. It is probable that the impetus for the development of compounds possessing properties of surface activity was furnished by the scarcity of fats for soapmaking in Germany during the First World War. During this period a considerable amount of experimental work was done in the search for substitutes for soaps. However, satisfactory products were not obtained until later with the development of the sodium alkyl sulfates. The production of these was limited until new techniques could be developed for converting fats into fatty alcohols by a process that involved subjecting them to extremely high pressures of 10,000 to 15,000 lb. per sq. in.

It has been estimated that at the present time over a thousand wetting agents are being marketed in this country under various trade names. The chemical structure of these compounds varies widely, but they usually are compounds of relatively high molecular weight and complicated structure. One characteristic common to all of them is that they have the ability to alter the surface tension of liquids (or the interfacial tension of mixtures of liquids) with which they are mixed, a property upon which their

[1] ANON. *Time, The Weekly Newsmagazine* No. xxxiv (1942), p. 32.

use depends. Not only do they change the surface tension of liquids, but they assist in overcoming the lack of attraction of liquid for solid, solid for solid, gas for liquid, and gas for solid. Because of their versatility, they are found useful in almost any industry where two or more substances are required to be mixed.

A few industrial applications will serve to illustrate the usefulness of these agents. In textile manufacture, they are used as an aid in securing rapid penetration of the fabrics by the dye solution; they are also employed in moth-proofing and in flame-proofing materials. They are widely used in the rubber industry to assist in dispersing pigments and sulfur in the rubber latex before vulcanizing. They are employed in metallurgy, where they assist in the pickling (cleansing with an acid bath) of castings; in the spreading of soldering fluxes; in the cleaning of metallic surfaces prior to electroplating; and in wetting ore particles in the separation of ores by the flotation process. In the food industry, these agents have been found useful in removing arsenic and other poisonous sprays from fruits and vegetables. They are widely used in the manufacture of paints, enamels, and printing inks, where they serve to improve the spreading qualities of these products. They have been found to increase the solvent action of liquids and solutions used in dry cleaning, and in laundering, they have been substituted wholly, or in part, for soap.

When compared with soaps, wetting agents have the advantages of being active in the presence of acids, in hard water, and in cold water. The public has become accustomed to the use of a few of these agents, which have been marketed under such trade names as Dreft or Drene. More recent investigations seem to indicate that these products may play a useful role in increasing the penetrating power of antiseptic agents which may find application in preoperative disinfection of the skin and the cleansing of superficial wounds or may be used in mouthwashes, dental preparations, nasal sprays, gargles, etc. There even appears to be some indication that certain of these agents may possess marked antiseptic properties in their own right.

No attempt is made in this brief discussion to consider the theoretical aspects of wetting agents or to explain how they function, except to indicate that, for the most part, the effects are

due to their tendency to reduce surface and interfacial tensions. An extended discussion would require an understanding both of organic chemistry, in order to comprehend the chemical nature of the substances, and of physical chemistry, in order to follow the theoretical explanation of their actions. The number of these products is so great and their chemical properties are so diverse that few generalizations may be drawn. The uses and applications of individual products have necessarily depended principally on experimental results obtained in detailed studies of a particular substance. For those interested in securing more information concerning these agents, it is suggested that some of the references cited at the end of this chapter be consulted.

Although the names of the compounds may have little significance except for those students who understand the nomenclature of organic chemistry, a few of the substances that have been used or recommended for use as surface-active agents will be listed here. The list is incomplete and perhaps should not be considered even representative, since the selection has been made more or less at random. This field of development is so recent and is increasing so rapidly that the data have not yet been well organized. Among the many substances that have been mentioned for special uses because of their properties as surface-active materials are the following: butyl cyclohexonal carboxylic acid, cetyl sulfate, cholesterol acetate, ethylene glycol-ditolyl ether, methyl cellulose, monostearyl glycol, monostearyl glycerol, octyl aminoethanoldiethylbenzyl ammonium chloride, polyvinyl acetate, resin soaps, salts of isopropyl tetrahydronaphthalene carboxylic acid, sodium dicresyl phosphate, sodium ditolyl phosphate, sodium lauryl sulfate, sulfonated benzylamylbutyl naphthalene, sulfonated benzylbutyl naphthalene, sulfonated cyclohexyl naphthalene, sulfonated products of lauryl alcohol, sulfonated products of myristyl alcohol, sulfonated phenylethyl naphthalene, triethanolamine, and trioxyethylamine stearate.

STUDY QUESTIONS

1. Distinguish between specific gravity and density.

2. State the principle of Archimedes as applied (*a*) to floating bodies, (*b*) to sinking bodies.

3. What is a hydrostatic balance?

4. Explain why no calculations are required in determining the specific gravity by the use of the Westphal balance.

5. Explain the difference between the constant-weight and the constant-volume types of hydrometer.

6. What are the special uses for (*a*) the saccharometer, (*b*) the lactometer?

7. Explain the principle involved in the determination of the specific gravity of liquids with the Fisher-Davidson apparatus.

8. What weighings are essential to the determination of the specific gravity of a solid that is lighter than water and insoluble in water?

9. What procedure should be followed in determining the specific gravity of a solid substance, heavier than water but soluble in water?

10. What procedure may be used for determining the specific gravity of a solid substance in powdered form that is heavier than and insoluble in water?

11. What is specific volume, and what is its relationship to specific gravity?

12. What are the physical characteristics of a liquid (*a*) of high viscosity, (*b*) of low viscosity?

13. What is meant by relative viscosity?

14. What is absolute viscosity?

15. What relationship exists between absolute viscosity and kinematic viscosity?

16. What is meant by optical refraction?

17. Define index of refraction.

18. What is molecular refraction?

19. What difference is noted in the units in which readings are obtained with the Abbe and the dipping refractometers?

20. What are the ranges of the readings that may be obtained with each of the instruments mentioned in the preceding question?

21. What is plane-polarized light?

22. What is a Nicol prism, and what effect does it have on ordinary light?

23. What characteristic of molecular structure gives rise to optical rotation in organic compounds?

24. Define specific optical rotation.

25. How may the known specific optical rotation for a given pure substance be used to determine the strength of impure samples of the same substance?

26. What special scales of calibration are used for saccharimeters, and what special advantages do they offer?

27. What are the principles upon which colorimetric determinations are based?

28. Explain briefly the principles of operation of a colorimeter of the Duboscq type.

29. What advantages are claimed for the electrophotometer over the colorimeter in making colorimetric determinations?

30. What is meant by surface tension?

31. Distinguish between cohesion and adhesion.

32. What is meant by capillarity?

33. Name three methods by which surface tension may be measured.

34. How are the values for surface tension expressed?

35. What relationship exists between the rise of an aqueous liquid in a capillary tube and the diameter of the tube?

36. Why do drops of a falling liquid tend to assume spherical form?

37. How should the meniscus of a liquid contained in a burette or pipette be read in order to avoid error in measurement?

38. What is meant by interfacial tension?

39. What characteristic do all the so-called "wetting agents" have in common?

40. Name some of the typical uses of wetting agents in manufacturing processes.

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CHAPTER IX

THEORY, GENERATION, AND CONTROL OF HEAT

The early alchemists observed that heat is always associated with the process of combustion. Although the nature of chemical changes during combustion was not understood, since at this point in the development of chemical knowledge only four elements were believed to exist, namely, fire, earth, air, and water, many explanations of the phenomenon of heat were offered.

The Phlogiston Theory.—Although the terms **element** and **combustion** were given many and varied interpretations, the **phlogiston** (from the Greek *phlogistos*, meaning burnt, inflammable) theory,[1] originally advanced by Johann Joachim Becher (1635–1682) and later elaborated by Georg Ernst Stahl (1660–1734), was the first to have a significant influence upon the development of chemistry. According to Becher, all inorganic substances consist of three "earths," the mercurial, the vitreous, and the combustible, which he later called *terra pinguis*. He held that, when substances are burned or calcined, the combustible earth escapes. Stahl adopted and expanded this idea, advancing the theory that all substances capable of burning contain a substance which he called phlogiston and that this is given off during the process. It was assumed that those substances which burn easily contain a high proportion of phlogiston and that the combustion is accompanied by the evolution of large amounts of heat, with the result that the residue is correspondingly small. Thus, it can be seen that the phlogiston theory was based upon the conception of the property of combustibility or inflammability as a material and ponderable substance.

Despite the efforts of many investigators, phlogiston was never isolated, although hydrogen, which was discovered by Cavendish[2] in 1766, was thought for a time to be this important substance.

With the discovery of many of the elements, facts began to accumulate that tended to oppose the phlogiston theory. It was shown that metals subject to combustion gain rather than lose weight. At first, phlogistonists denied this but later attempted to explain it by assuming that phlogiston possesses "negative weight." It was also pointed out that combustion

[1] E. KREMERS and G. URDANG. "History of Pharmacy," J. B. Lippincott Company, Philadelphia, 1940, p. 338.

[2] "The Encyclopedia Americana," Americana Corp., New York, 1940, Vol. 21, p. 784.

does not occur except in the presence of air, but this was explained by saying that the air is required to carry away the phlogiston which is liberated.

It was Lavoisier who finally succeeded in overthrowing the phlogiston theory. He was able to show by careful weighings that a metal gains weight upon combustion and that the increase in weight is exactly equal to that lost from the surrounding air. Later, after the discovery of oxygen by Scheele and Priestley, both of whom were advocates of the phlogiston theory, Lavoisier proved that it is this element which combines with the metal to bring about the increase in weight.

The Caloric Theory.—With the overthrow of the phlogiston theory, new ideas were advanced. According to a view that was widely accepted, heat was assumed to be an imponderable fluid, called **caloric,** which flows into and out of bodies, thus producing the effects of heating and cooling. It was not until the early part of the nineteenth century that the caloric theory was abandoned, largely as the result of experiments of Davy and Rumford[1] in which heat was created directly by mechanical energy.

The Molecular-motion Theory.—In place of the caloric theory, the molecular-motion theory has been accepted generally. According to this theory, heat is only the manifestation of the agitation of the molecules of matter.[1] Although the molecules are extremely small, each has a definite size and weight for a given substance. It has been estimated, for example, that a molecule of water has a diameter of approximately 1/140,000,000 in. Despite the fact that molecules are extremely small in size, the velocity of their vibrations, even at ordinary temperatures, is very high. It has been estimated that, in air, in which the molecules move about in straight lines until they collide with other molecules, a speed of approximately 1,470 ft. per sec. is attained at 0°C. The average length of the path between successive encounters, called the **mean free path,** has been calculated to be approximately 1/277,000 in. It has been estimated that the number of molecules in a cubic inch of air is 433 trillion and that each molecule experiences approximately five billion collisions per second.

Expansion of Solids, Liquids, and Gases.—The molecules of a substance are attracted to one another by a force called **cohesion.**

[1] E. R. VON NARDROFF. "The Encyclopedia Americana," Americana Corp., New York, 1940, Vol. 14, p. 41.

The pressure of the atmosphere also assists in holding the molecules of the body together. Heat is opposed to both these forces. The effect upon the vibration of the molecules produced by the application of heat is to cause them to drive one another farther apart. Consequently, an increase in temperature of a body always results in its expansion.

Solids.—In the case of solid substances, in which the force of cohesion is very great, the expansion produced for a given increase of temperature is relatively small, especially if the test is made at a low temperature. At higher temperatures, at which the mutual attraction of the molecules (cohesion) has been decreased because the intervening space has become greater, an increase in temperature generally produces a correspondingly greater expansion.

In measuring and comparing the effect of heat upon the expansion of a body, the expression **coefficient of linear expansion**

TABLE XII.—COEFFICIENTS OF LINEAR EXPANSION OF SOLIDS[1]

Substance	Coefficient	Substance	Coefficient
Aluminum	0.0000222	Lead	0.0000271
Cast iron	0.0000106	Platinum	0.0000093
Copper	0.0000167	Porcelain	0.0000041
German silver	0.0000183	Silver	0.0000192
Glass tubing	0.0000083	Steel	0.0000123
Gold	0.0000147	Wrought iron	0.0000121
Invar (Guillaume's nickel steel)	0.0000087		

[1] These values were selected from a table given in the "The Encyclopedia Americana," Americana Corp., New York, 1940, Vol. 14, p. 42.

is used. This term may be defined as the fraction of its length represented by the expansion produced when a substance is elevated in temperature through 1°C. Since the length of a bar of any substance varies with the temperature, the length at a temperature of 0°C. is taken as the standard of comparison. The coefficients of linear expansion of a number of substances are found in Table XII.

By referring to the appropriate values given in Table XII, it can be seen that a bar of aluminum, exactly 1 M. long at 0°C.,

would measure 1.0000222 M. at 1°C., or 1.00222 M. at 100°C. Similarly, a bar of steel, exactly 1 M. long at 0°C. would measure 1.0000123 M. at 1°C., or 1.00123 M. at 100°C.

It will be noted that the value of the coefficient for glass is very close to that for platinum. Advantage is taken of this fact in the construction of incandescent electric lamps and in the manufacture of scientific instruments in which it is necessary for wires to pass through glass to form airtight junctures. In manufacture, the glass around the hole is softened by heat until it flows closely around the hot platinum wire. If the coefficient for platinum were appreciably higher than that for glass, the platinum would contract upon cooling more rapidly than the glass and the result would be a leaky joint.

It will also be noted that the coefficient of expansion of Guillaume's nickel steel, known as Invar, is extremely small. This fact makes this alloy especially useful for the construction of clock pendulum rods, surveying instruments, standard measures of linear dimensions, and many other instruments in which a high coefficient of expansion would introduce a source of error.

Liquids.—In the liquid phase of matter, the molecules are so nearly free from the effects of cohesion that they are able to roll about one another and change positions within the liquid at will. As in the solid phase, the greatly reduced force of cohesion is aided by atmospheric pressure or other pressure in preventing the molecules from flying directly apart. Because of the fact that resistance to expansion is so greatly reduced, liquids show relatively higher degrees of expansion with elevation in temperature than do solids.

The term **coefficient of cubical expansion** is used in measuring the expansion of liquids. This is defined as that fraction of its volume by which a liquid expands when its temperature is raised through 1°C. as compared with its original volume at 0°C. The cubical coefficient of a substance is three times as great as its linear coefficient since the effect of expansion is measured in terms of the three dimensions of a liquid. If, however, the liquid is confined in a tube of unchanging dimensions so that it is restrained from expanding except in one direction, as, for example, in the case of mercury confined in a thermometer tube, the effect of expansion in this one direction would be three times

as great as it would be if the liquid were allowed to expand proportionately in all three dimensions. The coefficients of cubical expansion of a few liquids are listed in Table XIII.

The abnormal behavior of water is noteworthy. Very careful measurements have shown that water attains its greatest density at the temperature of 4°C., rather than at the temperature of its freezing point of 0°C. Whenever water at 4°C. is either warmed or cooled, it expands and becomes lighter. This fact is of considerable biological significance, since otherwise the water in lakes would freeze in winter not only at the surface but solidly from top to bottom, thus destroying aquatic life. It will be recalled that this anomaly in the behavior of water was mentioned in connection with the discussion of the metric system in Chap. VII.

TABLE XIII.—COEFFICIENTS OF CUBICAL EXPANSION OF LIQUIDS[1]

Liquid	Coefficient	Liquid	Coefficient
Alcohol	0.00112	Olive oil	0.00072
Glycerin	0.00050	Petroleum	0.00095
Mercury	0.000182	Water	0.00021

[1] Selected values from a table in "The Encyclopedia Americana," Americana Corp., New York, 1940, Vol. 14, p. 42.

Transmission of Heat.—Since heat is but one form of energy, it follows that it may be converted into other forms. According to the first law of thermodynamics, whenever heat energy is transformed into mechanical energy (or the reverse), for each unit of the energy that disappears there is always a perfectly definite and constant quantity of the new kind of energy.

A vast number of experiments were conducted by Joule for the purpose of determining the mechanical equivalent for heat, which he expressed as the number of units of mechanical energy that are equivalent to one unit of heat. According to the findings that he reported about 1840, 1 lb. of water is raised by 1 Fahrenheit degree by the expenditure of 772 ft.-lb. of energy. The foot-pound may be defined as the amount of work done in overcoming by raising vertically, through a distance of 1 ft., the resistance equal to the weight of 1 lb. of matter. Later measurements made by Rowland in 1879, working with much better

equipment, led to a revision of this value. It now appears that the heat required to raise the temperature of 1 lb. of water 1°F. is equivalent to 778 ft.-lb. of work. This is equal to the energy required to lift 1 lb. of matter 778 ft., or 778 lb. of matter 1 ft.

The metric equivalent of the mechanical equivalent of heat is expressed in terms of kilogram-meters and may be defined as the quantity of energy required to heat 1 Kg. of water 1°C. It should be noted that this value is not identical with the mechanical equivalent of heat expressed in foot-pounds, since the definition of the former value is based upon the kilogram instead of the pound and upon 1 centigrade degree instead of 1 Fahrenheit degree. Furthermore, the quantity of energy is expressed in kilogram-meters instead of foot-pounds, this unit being the energy required to overcome the resistance offered by elevating 1 Kg. of matter 1 M. The metric mechanical equivalent of heat may be derived from the quantity expressed in foot-pounds by the following calculations:

$$778 \times 1.8 \times 2.2189 \times 0.3048 = 947.1$$

In this equation, the value 1.8 (or $\frac{9}{5}$) is the correction for the difference in the two thermometer scales, 2.2189 represents the number of avoirdupois pounds equivalent to 1 Kg., and 0.3048 is the factor for converting feet to meters. It should be observed that the calculation indicated increases the quantity of energy to correspond to the greater weight of water to be heated and the greater value of the centigrade degree, but the result is in terms of pound-meters. It is therefore necessary to convert this to kilogram-meters by the calculation

$$\frac{947.1 \times 1}{2.2189} = 426.84 \text{ Kg.-M.}$$

This indicates that the mechanical energy equivalent to the quantity of heat required to raise the temperature of 1 Kg. of water 1°C. is equal to the mechanical energy sufficient to raise 1 Kg. of matter 427 M., or 427 Kg. 1 M.

The second law of thermodynamics was proposed by Clausius and in its simplest form implies that heat tends to pass from a hotter body to a colder one, and not vice versa. As a corollary to this law, it follows that more heat cannot be transmitted from

the hotter body than that required to establish an equal temperature between the two bodies. In accordance with the law of Clausius, it follows that whenever two bodies of different temperatures are brought in contact or proximity with each other, heat is transferred from the body with the higher temperature until a thermal equilibrium is attained. This transfer is made by **conduction, convection,** or **radiation,** or by some combination of these methods.

Conduction.—The transmission of heat by direct contact of two bodies of different temperature levels or in one body whose

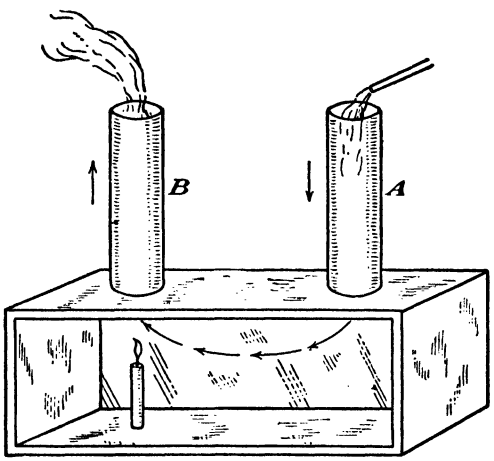


FIG. 50.—Diagram of convection currents. (*From N. H. Black, "An Introductory Course in College Physics," The Macmillan Company, New York,* 1935.)

parts are at different temperatures is known as conduction. The flow of heat through an iron rod is an example of heat transmission by conduction. Substances show a wide variation in their capacities to conduct heat. Metals are, as a rule, good conductors. Wood, air, and liquids are relatively poor conductors.

Convection.—The transmission of heat by the circulation of a liquid or a gas is known as convection. It is this principle which is employed in most systems for the heating and ventilation of buildings. Any gas or liquid expands when heated, thus increasing in volume and decreasing in density. The lighter fluid is pushed upward by the heavier surrounding fluid, setting up a

circulation of convection currents. It should be noted that convection differs from conduction in that the heat transfer is effected by the movement of particles of matter, whereas in conduction the transfer is made by molecules adjacent to each other, no change in the relative positions of the molecules being involved.

Radiation.—Radiation is the transfer through space of energy that, when absorbed by matter, appears as heat. The sun is the chief source of radiant energy. Some substances, such as air and glass, permit the sun's heat rays to pass through them almost undiminished by absorption. Thus, they are not warmed appreciably by the sun's rays. Such substances are spoken of as being "transparent to heat." Other objects, such as water, metals, etc., do not permit the heat rays to pass through them, and they are warmed by any heat rays that fall upon them. Such substances are said to be "opaque to heat." It is believed that heat rays, like light rays, travel in straight lines. They may be reflected with mirrors or brought to a focus by means of a lens or burning glass.

Evaluation of Heat.—The measurement of heat may be of two kinds, qualitative and quantitative. The qualitative measurement deals with the intensity of heat and is usually recorded in terms of degrees of some thermometer scale. On the other hand, the temperature or intensity is no indication of the total amount of energy or quantity of heat represented. Since heat is not a substance, but a form of energy, it can be evaluated only by measuring the effects that it will produce. Special units, known as the **calorie** (for the metric system) and the **British thermal unit** (for the English system), have been established for this purpose. The intensity of heat, expressed in degrees, is somewhat analogous to the pressure at which water is delivered at the tap, while the quantity of heat, in calories or British thermal units, may be compared to the number of gallons of water consumed, as shown by the water meter.

Thermometers.—The instrument most commonly used for determining the intensity of heat, for ordinary ranges of temperature, is the thermometer. Although there are several types of scale, such as the Fahrenheit, centigrade, Reaumur, and absolute, all forms of thermometer depend upon the fact that most liquids,

such as mercury and alcohol, expand when heated and contract upon cooling. Since mercury freezes at −39°C., the thermometer used for very low temperatures is usually filled with alcohol, which is commonly colored with a suitable dye. On the other hand, alcohol is unsuitable for use in the higher temperature ranges because of its relatively low boiling point (78°C.), and mercury (which boils at approximately 357°C.) is used for this purpose. Regardless of the liquid used in the thermometer, the construction is essentially the same for both types. Fundamentally, the thermometer consists of a capillary tube, from which the air has been exhausted and which has a reservoir or bulb for reserve liquid. The stem of the instrument is provided with graduations, either etched directly on the glass or placed on a glass, paper, metallic, or wooden scale attached to the thermometer tube.

For temperatures above the limits of the mercury thermometer, the air thermometer is used. This instrument measures the change in pressure of a known volume of air with elevation in temperature. For still higher ranges the variation in the electrical resistance of a conductor is measured, or the electromotive force of a thermoelectric couple, one of whose junctions is maintained at constant temperature while the other is exposed to the temperature to be measured.

The Fahrenheit Scale.—Among English-speaking people, the thermometer devised by Fahrenheit in 1714 is still in common use in reporting weather data and in the control of temperature for many technical and industrial processes, but in scientific work it has been replaced by the centigrade thermometer. Originally the Fahrenheit scale was based upon two reference points, (1) the temperature reached with a mixture of ice and an excess of salt and (2) the temperature of the human body.[1] Fahrenheit, supposing that the low temperature reached with the ice and salt mixture was the lowest that can be reached, assigned the zero-degree reading to this point.

Somewhat earlier, Newton had suggested that the range between the temperature of ice and that of the human body should be considered as 12°. He was probably influenced in his choice by the fact that the dozen was at that time a commonly

[1] "The Encyclopedia Americana," 1940, Vol. 10, p. 711.

used numerical unit. Fahrenheit accordingly multiplied this number of divisions by 8, thus assigning to the upper reference point the value of 96°. His choice of the lower reference point, obtained with the salt and ice mixture, was probably due to his belief that the freezing point of water is not a constant value; he was led into this false assumption by the fact that it is possible under certain conditions to supercool water below its freezing point. By subdividing the space between the reference points into 96 equal divisions and extending the scale upward and downward in proportion, the values for the Fahrenheit scale were established. When tested with the Fahrenheit thermometer, the freezing point of water is found to be 32° and its boiling point 212°. Therefore, the range in temperature between these two points covers 180 scale divisions.

The Centigrade Scale.—Shortly after the introduction of the Fahrenheit thermometer, it was recognized that the freezing point and the boiling point of water afford more accurate and useful primary standards than the reference points selected by Fahrenheit. Accordingly, Celsius, in 1740, proposed the centigrade scale in which these two constants served as the lower and upper limits and were assigned the values of 0 and 100°, respectively. As previously mentioned, this scale is used in connection with all scientific work and is the official thermometer scale adopted by the Pharmacopoeia.

The Reaumur Scale.—For certain types of industrial process, notably in brewing, still a third type of thermometer scale, devised by Reaumur in 1730, has been used to a limited extent in northeastern Europe. As in the centigrade scale, the reference points are the freezing point and the boiling point of water. Although the freezing point is assigned the same value as in the centigrade scale (0°), the boiling point is shown as 80° instead of 100°. The Reaumur scale is not used in this country and is, therefore, of minor importance to our discussion. Since it occasionally becomes necessary, however, to make conversions from this system to the Fahrenheit or centigrade scale, the relationships among the various degrees should be understood. These are easily derived by noting the number of scale divisions between the freezing point and boiling point of water on the three instruments, namely, 180, 100, and 80, respectively, for the Fahrenheit, centigrade, and Reaumur scales. Accordingly, one Reaumur degree is equivalent to $\frac{5}{4}$ of a centigrade or $\frac{9}{4}$ of a Fahrenheit degree. Conversely, a centigrade degree is equivalent to $\frac{4}{5}$ of a Reaumur degree, and a Fahrenheit degree is equivalent to $\frac{4}{9}$ of a Reaumur degree. To complete the relation-

ships, it should also be noted that the Fahrenheit degree is equivalent to $\frac{5}{9}$ of a centigrade degree and one centigrade degree is equivalent to $\frac{9}{5}$ of a Fahrenheit degree.

Conversion of Thermometer Readings.—It is quite unnecessary to memorize rules for making a conversion from one thermometer scale to another, since the relationship may readily be reasoned out if the values for the reference points, the freezing point and the boiling point of water, are known. The chief source of confusion in making such conversions lies in the fact that the freezing point of water on the Fahrenheit scale is 32°. Since this is the reference point equivalent to 0° on either of the other scales, for readings above 32 only the number of scale divisions in excess of 32 are to be multiplied by the appropriate factor. On the other hand, if the readings are below 32°F., the number of scale divisions between the observed reading and 32° are to be converted. If the readings are below 0 on the Fahrenheit scale, the 32 scale divisions between 32 and 0 must be added to the observed reading before the conversion is made. Conversely, suitable adjustment must be made to all conversions made from the other thermometer scales to the Fahrenheit scale by adding or subtracting the 32 scale divisions, as may be required, in order to adjust the converted reading to the proper position on the Fahrenheit scale.

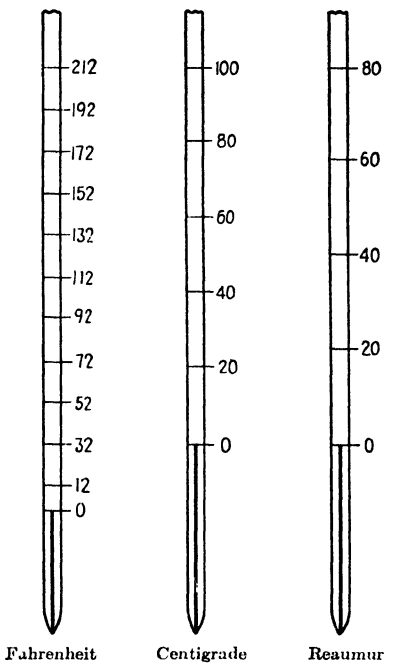


FIG. 51.—Comparison of the Fahrenheit centigrade, and Reaumur thermometer scales.

The application of the fundamental relationships used in making thermometric conversions is illustrated in the following examples:

1. *Centigrade to Fahrenheit.*

a. Convert 80°C. to the corresponding reading on the Fahrenheit scale.

$$80 \times \tfrac{9}{5} = 144 + 32 = 176°\text{F.}$$

b. Convert −50°C. to the equivalent reading on the Fahrenheit scale

$$50 \times \tfrac{9}{5} = 90$$
$$90 - 32 = 58$$

Hence, the reading is −58°F.

2. *Fahrenheit to Centigrade.*

a. Convert 95°F. to the centigrade reading.

$$95 - 32 = 63 \times \tfrac{5}{9} = 35°\text{C.}$$

b. Convert −49°F. to the centigrade reading.

$$49 + 32 = 81 \times \tfrac{5}{9} = 45$$

Hence, the reading is −45°C.

3. *Reaumur to Fahrenheit.*

a. Convert 60°R. to the Fahrenheit reading.

$$60 \times \tfrac{9}{4} = 135 + 32 = 167°\text{F.}$$

b. Convert −36°R. to the Fahrenheit reading.

$$36 \times \tfrac{9}{4} = 81 - 32 = 49 \text{ below the freezing point of water.}$$

Hence, the reading is −49°F.

4. *Fahrenheit to Reaumur.*

a. Convert 113°F. to the corresponding reading on the Reaumur scale.

$$113 - 32 = 81 \times \tfrac{4}{9} = 36°\text{R.}$$

b. Convert 14°F. to the equivalent reading on the Reaumur scale.

$$32 - 14 = 18 \times \tfrac{4}{9} = 8$$

Hence, the reading is −8°R.

5. *Centigrade to Reaumur.*

Convert 65°C. to the corresponding Reaumur reading.

$$65 \times \tfrac{4}{5} = 52°\text{R.}$$

6. *Reaumur to Centigrade.*

Convert 40°R. to the equivalent centigrade reading.

$$40 \times \tfrac{5}{4} = 50°\text{C.}$$

The Absolute Scale.—In addition to the three thermometer scales already mentioned, a fourth scale known as the Kelvin or absolute scale is used in scientific work. This scale was derived by observing the behavior of gases upon cooling. Most gases, at atmospheric pressure, undergo a decrease in volume corresponding to $\frac{1}{273}$ of their volume at 0°C., for every degree centigrade of decrease in temperature. If this shrinkage in volume were to continue uniformly at this rate, we could predict that the volume of a gas would become zero at a temperature of −273°C. Actually, this does not occur since no gas has been found that does not liquefy long before this low temperature is reached, and at this point it ceases to follow the rule for the

behavior of gases. The temperature of −273°C. is designated as **absolute zero.** It is this behavior of gases which serves as the basis for Charles's law, which may be stated as follows: "At constant pressure, the volume of a gas varies directly as the absolute temperature." Since the temperature interval on the absolute scale is identical with that of the centigrade scale, degrees absolute may be calculated by the simple equation

$$°A. = °C. + 273°$$

Pharmacopoeial Requirements for Thermometers.—The general and specific requirements for thermometers that are to be used in conducting official tests are the subject of a special monograph[1] in the Pharmacopoeia, and are given below.

Thermometers for Pharmacopoeial Testing.—These thermometers conform to the specifications of the American Society for Testing Materials, the specifications being designated as follows:

TABLE XIV

Type	Purpose	A.S.T.M. designation
I	General	E1 (1C-39)
II	General	E1 (2C-39)
III	Petrolatum and other Type III melting points	E1 (14C-39)
IV	Determining kinematic viscosity	E1 (18C-39)
V	Determining the titer of fatty acids	E1 (36C-41T)

The stem of each thermometer shall be made of suitable thermometer tubing and shall have a plain front and an enameled back. All graduation lines, figures, and letters shall be clear-cut on the glass stem and shall be uniformly well filled with insoluble colored pigment.

The bulb of each thermometer shall be made of Corning normal or equally suitable thermometric tubing.

The thermometers shall be so thoroughly annealed that there will be no appreciable change in their indications after long-continued exposure to the highest temperature on the scale.

[1] "The Pharmacopoeia of the United States of America," twelfth revision, p. 622, 1942.

For further details regarding the standardization of these thermometers, reference should be made of A.S.T.M. Standards, Part III, American Society for Testing Materials.

TABLE XV.—THERMOMETERS FOR PHARMACOPOEIAL TESTING

Thermometer type	I	II	III	IV	V
Liquid	Mercury	Mercury	Mercury	Mercury	Mercury
Filling above liquid	Nitrogen	Nitrogen	Nitrogen	Nitrogen	Nitrogen
Temperature range	−20 to +150°C.	−5 to +300°C.	38 to 82°C.	34 to 42°C.	−2 to +68°C.
Subdivisions	1°C.	1°C.	0.1°C.	0.1°C.	0.2°C.
Total length	303-307 mm.	379-383 mm.	365-371 mm.	252-256 mm.	385-390 mm.
Stem diameter	6.0-7.0 mm.	6.0-7.0 mm.	6.0-7.0 mm.	6.0-7.0 mm.	6.0-7.0 mm.
Bulb diameter	5.0-6.0 mm.	5.0-6.0 mm.	Not greater than stem	5.0 to diam. of stem	5.5-7.0 mm.
Bulb length	19-25 mm.	10-15 mm.	Not over 28 mm.	25-35 mm.	15-25 mm.
Bottom of bulb to graduation line at distance	−18°C.	0°C.	38°C.	34°C.	−2°C.
	90-100 mm.	100-110 mm.	105-115 mm.	135-150 mm.	50-60 mm.
Top of thermometer to graduation line at distance	150°C.	300°C.	82°C.	42°C.	68°C.
	20-35 mm.	25-50 mm.	25-40 mm.	20-35 mm.	20-35 mm.
Longer graduation lines at each	5°C.	5°C.	0.5°C.	0.5°C.	1°C.
Graduations numbered at each multiple of	10°C.	10°C.	1°C.	1°C.	2°C.
Immersion	76 mm.	76 mm.	79 mm.	Total	45 mm.
Scale error at any point, when standardized, shall not exceed	0.5°C.	1°C.	0.1°C.	0.1°C.	0.2°C.

The Care and Handling of Thermometers.[1]—In the handling of thermometers, it is often found necessary to manipulate the mercury within the capillary, in order to reunite with the main column a part of the mercury which has become separated, to remove gas bubbles from the mercury in the bulb or stem, or to separate a mercury thread for use in calibrating. There are four operations usually resorted to in manipulating the mercury, *viz.*, (a) warming, (b) cooling, (c) tapping on the end, and (d) tapping on the side of the thermometer.

Warming the bulb of a thermometer may be done in water or oil or in air high above a gas or alcohol flame, but great care must be taken, especially with high temperature thermometers, not to heat the bulb to a temperature higher than the thermometer is intended to measure. The upper end of a thermometer stem may be warmed over a Bunsen burner if this is done very

[1] E. F. COOK and CHARLES H. LAWALL. "Remington's Practice of Pharmacy," J. B. Lippincott Company, Philadelphia, 8th ed., 1936, p. 102. Extract from *Natl. Bur. Standards, Circ.* 8, 3d ed. (August, 1921).

gradually. When the thermometer is warmed over a flame, it should be rotated about its axis.

Cooling may be accomplished in cold water, ice, a freezing mixture, or carbon dioxide snow, but such cooling should not be attempted while the thermometer bulb is still hot to the touch.

Tapping or striking a thermometer on the end must be done carefully at all times, and much more so when the bulb is only partially filled with mercury and the thermometer is inverted. This tapping may be soft, as when the thermometer is held vertically and the hand (not the thermometer) is struck on the table, or it may be sharp, as when the thermometer is held vertically and struck downward on a pad of paper.

Tapping on the side of a thermometer may be done softly with the hand or sharply with a pencil. Either must be done with care, as there is danger of breaking the stem. Different thermometers require different treatment, but the following procedure may serve as a guide in the manipulation of thermometers not filled with gas under pressure.

To remove mercury from the upper bulb when it is partially full, hold the thermometer vertically, bulb down. Tap softly on the side near the top and softly on the end, to bring the mercury to the lower part of the upper reservoir. Then try both tapping softly and sharply, on the end, and if this fails to bring the mercury down the stem, warm the bulb until the mercury rises and unites with that in the reservoir. Cool very slowly and probably the mercury will all come down. If not, try again, cooling more slowly.

To remove mercury from the upper reservoir when this is completely full or when the mercury persistently stays at the top reservoir, warm the upper end carefully over a Bunsen flame, beginning at the extreme tip. The mercury will be driven down the capillary by its own vapor pressure. If small mercury globules are left, warm a little more and they will condense farther down. Wait until the upper end cools to a temperature comfortable to the hand. Warm the lower bulb until the mercury rises and collects the small globules.

To find whether there is any residual gas in the thermometer bulb, warm the bulb until at least a few centimeters of mercury appear in the capillary; if mercury is already there, do not warm. Invert the thermometer, and see whether the mercury runs down. If not, there is probably no gas in the bulb. If the mercury runs down, let it run a few centimeters and look for a bubble in the bulb. Right the thermometer, and see whether this bubble entirely disappears when the mercury returns to the bulb. If this bubble disappears, no significant amount of gas is present.

To remove gas when found, invert the thermometer and run some mercury into the capillary. Right the thermometer and tap sharply on the side and on the end to bring the gas to the top of the bulb before the mercury all returns. Cool the bulb as much as possible, tapping sharply on the end when cold. Invert the thermometer and tap very softly on the end to bring down the mercury which is still separated by the air bubbles from that in the bulb. When this has come down, either tap "sharply" or warm to

bring down the mercury from the bulb, but do not let the separated thread get into the upper bulb until the main mercury column is ready to join it. Get the two separated parts to join in any convenient enlargement or in the upper reservoir. Right the thermometer or hold it at an angle, with the top higher, and let the mercury run slowly into the bulb, watching carefully the point where the bubble is left, to be sure that the column does not separate. If the bubble begins to enlarge, run the mercury more slowly.

FIG. 52.— Anschütz thermometer.

Bubbles can often be removed, even from high temperature thermometers, which are filled under pressure, provided there is an enlargement in the stem (*e.g.*, between the zero and 300°C. mark). If there is no such enlargement the gas can sometimes be removed by long, continued sharp tapping on the end, or sometimes by freezing the mercury by means of CO_2 snow, then warming the bulb (from the bottom) rapidly against the hand. Mercury will not break the bulb on freezing, as it does not expand.

Types of Thermometer.—Many forms of thermometer have been designed for special uses. The modifications introduced have, in some cases, been made with the object of increasing the degree of accuracy of the instrument. In other cases, the purpose has been to adapt a given thermometer to a special use. A few of the more important types of specialized thermometer are described briefly in the following sections.

The Anschütz Thermometer.—One of the objections to the use of the ordinary type of thermometer in the determination of melting and boiling points is the error introduced by the effect of the heat transmitted by conduction and radiation to the thermometer stem. In order to overcome this difficulty in melting-point determinations, it is usually necessary to attach an auxiliary thermometer, at a point halfway between the surface of the bath and the level of the supposed melting point of the substance, to the main thermometer, and calculate the emergent stem correction by applying a formula to the reading of the auxiliary thermometer that is obtained at the time of the end of melting of the sample being tested. The necessity for this correction is clear when it is remembered that the transmitted

heat causes the glass tube of the thermometer to expand, thus distorting it and destroying the accuracy of the thermometer scale.

In order to eliminate the necessity for making emergent stem corrections in melting-point and boiling-point determinations, the Anschütz type of thermometer has been developed. This consists essentially of a small capillary tube containing a column of mercury which is attached to a graduated milk-glass scale, the whole being sealed in a larger tube from which the air has been partly exhausted. The insulating effect of the partial vacuum that surrounds the thermometer tube is comparable to the effect obtained in the vacuum bottle, which employs the same principle.

Thermometers of this type covering the ordinary ranges of temperature are available in a single instrument, or in a series of seven instruments of overlapping ranges, covering the total range for the series of −10 to 360°C., graduated into $\frac{1}{5}$° divisions.

Differential Thermometers.—In calorimetry, molecular-weight determinations by the boiling-point method, and determination of the cryoscopic point in the adjustment of tonicity (osmotic pressure) of solutions intended for parenteral use, it is necessary for very small changes in temperature to be measured accurately. The ordinary thermometer is useless for such purposes. As implied by its name, the differential thermometer, of which the Beckmann instrument is the most common example, is especially designed for accurate measurements of very slight changes in temperature. The instrument consists of a capillary tube extending from the mercury bulb to an auxiliary scale and provided with a milk-glass scale, which covers a range from 5 to 6°C., subdivided into $\frac{1}{100}$° divisions. The auxiliary scale covers the range from −10 to 140°C.,

FIG 53.—Beckmann differential thermometer.

graduated in 2° divisions. The instrument can be set for any temperature within its limits by suitable manipulation of the columns of mercury.

Clinical Thermometers.—One of the most important special forms of thermometers is the clinical thermometer, commonly called a "fever thermometer" by the layman, which is used in determining the temperature of the body. Under normal conditions of health, the temperature of the human body, when measured by inserting the bulb of the thermometer beneath the

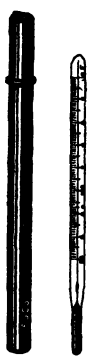


FIG. 54.—Clinical thermometer.

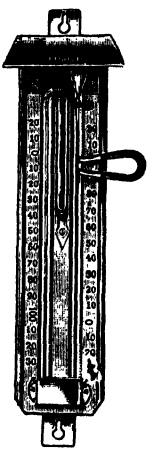


FIG. 55.—Maximum and minimum registering thermometer.

tongue, is 98.6°F. (37°C.). If the rectal temperature is taken, this is usually found to be about 1°F. higher. Temperature readings taken by inserting the thermometer in the axilla or in the groin usually are 0.5°F. lower than the temperature taken by mouth.

Clinical thermometers are usually triangular in cross section, the thickened wall of the thermometer stem serving to magnify the extremely fine column of mercury that is used in the instrument. This greatly facilitates the reading.

All clinical thermometers are of the self-registering type. That is, the capillary tube is provided with a slight constriction near the bulb of the thermometer, which causes the column of mercury to remain fixed in the position represented by the highest temper-

ature attained until it is shaken down. This operation is one that calls for some skill, and careless handling during this process often leads to breakage. One manufacturer of clinical thermometers has made available a device that is dependent upon centrifugal force for restoring the level of the mercury column and that is quite efficient in operation and in preventing breakage.

Clinical thermometers are usually listed as 1-min., 2-min., or 3-min. thermometers, the terms indicating the length of time required for adjustment of the column of mercury to the proper level for an accurate reading. Unless sufficient time is allowed for this adjustment to take place, according to the type of thermometer being used, the observed readings may be too low.

The Maximum and Minimum Registering Thermometer.—Figure 55 shows the maximum and minimum registering thermometer of the Sixe type. This instrument is intended for use in recording the daily maximum and minimum temperatures. It is graduated in the Fahrenheit system exclusively. It consists of a U tube, the high temperature being indicated at the top of one leg and the low temperature at the top of the other. Small metal floats rise with the column of mercury and remain fixed at the highest position attained by the column during the interval between settings of the instrument. These floats are reset by means of a small magnet, supplied with the instrument.

The U.S. Weather Bureau pattern thermometers are intended for the same purpose but are of different design and principle of operation. Separate instruments are provided, one for registering the minimum temperature and another for registering the maximum temperature. Automatic registration is accomplished by the use of a constriction in the capillary tube, applying the same principle as that used in the clinical thermometer.

Quantitative Units for Measuring Heat.—As indicated earlier in this chapter, the units employed for determining the quantity of heat represented by a given quantity of fuel are known as the **calorie** and the **British thermal unit.** When the term *calorie* is used without qualification, it is usually understood to mean the **gram-calorie** which is defined as the quantity of heat required to raise the temperature of 1 Gm. of water 1°C. For measurement of larger quantities, the **kilogram-calorie,** sometimes called the **large calorie,** is employed. This is defined as the quantity

of heat required to raise the temperature of 1 Kg. of water 1°C. This system of evaluating the quantity of heat is used exclusively in all types of scientific work. In Great Britain, and to a considerable extent in this country, the British thermal unit is used, especially in reporting the heating value of fuels. The British thermal unit, abbreviated B.t.u., is defined as that quantity of

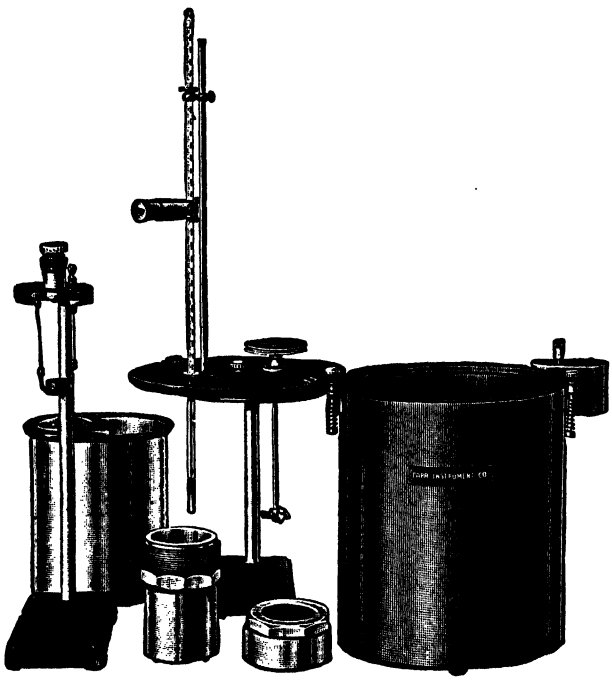


FIG. 56.—Oxygen-bomb calorimeter.

heat which is required to raise the temperature of 1 lb. (av.) of water from 60 to 61°F., the tests being made at sea level. Since 1 lb. is equivalent to 454 Gm. and 1 scale division on the Fahrenheit scale is equal to $\frac{5}{9}$ of a division on the centigrade scale, 1 B.t.u. is equal to $454 \times \frac{5}{9}$, or 252 cal. Conversely, division will show that 1 Kg.-cal. (or large calorie) is equivalent to 3.97 B.t.u.

Calorimeters.—The instrument used for determining the capacity of a substance to produce heat is called a **calorimeter.** The heating value is determined experimentally by burning a

sample of the material and determining the amount of heat that is absorbed in a known quantity of water placed in a jacket surrounding the combustion chamber. In actual practice, the determination is usually made by one of the following three methods: (1) the oxygen-bomb method, for solids and liquids; (2) the sodium peroxide method, for solids and liquids; (3) the gas combustion method, for vapor and gases.

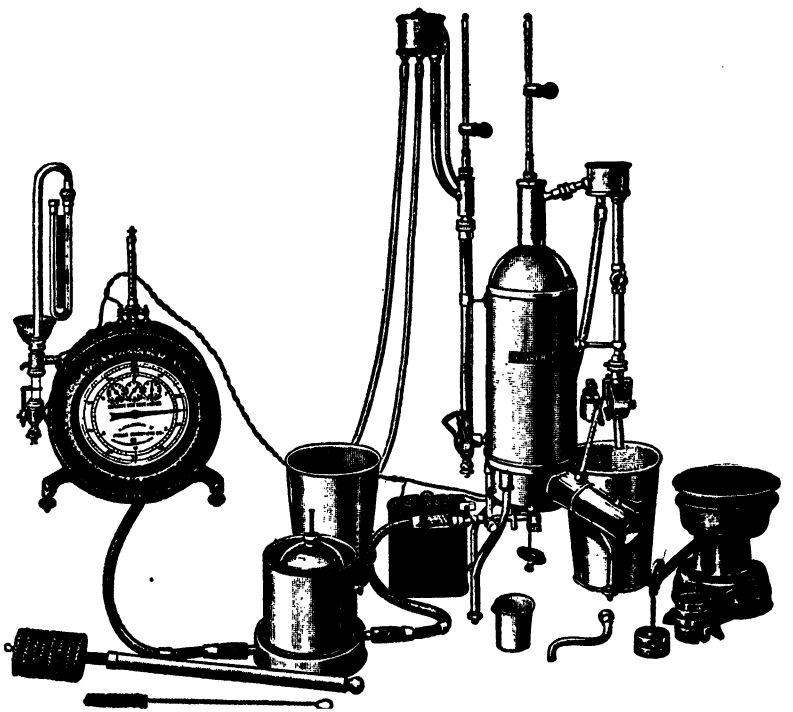


FIG. 57.—Gas combustion calorimeter.

Oxygen-bomb Method.—In this method, a weighed quantity of the solid material to be examined is compressed into a tablet. In the case of a liquid, this is absorbed by some substance such as napthalene, benzoic acid, or soft coal and then compressed. The liquid may also be tested directly by confining it in a thin-walled glass balloon. The sample is then ignited in an atmosphere of oxygen under pressure by means of an electrically heated wire. The heat evolved during combustion is absorbed

by a quantity of water of known weight contained in the jacket surrounding the combustion chamber. The jacket is carefully insulated to prevent loss of heat through radiation.

Sodium Peroxide Method.—In this method, the oxygen required for the combustion is derived from sodium peroxide, mixed with the sample to be tested. Sometimes an accelerator, such as potassium chlorate, benzoic acid, or naphthalene, is added to the charge to facilitate ignition. This method, although probably not quite so accurate as the oxygen-bomb method, has the advantage of permitting the combustion to take place at a relatively low pressure and in addition eliminates the need for a supply of gaseous oxygen under pressure.

Gas Combustion Method.—In this method, the vapor or the gas to be tested is passed at a measured rate of flow through a burner, the resulting heat being absorbed by water flowing at a measured speed through a jacket surrounding the combustion chamber. By noting the inlet and outlet temperatures of the water, the quantity of gas consumed, and the quantity of water used to absorb the heat, it is possible to calculate the heating capacity of the gas.

Specific Heat.—Different substances show a wide variation in their capacity to absorb heat. If, for example, equal weights of mercury and of water, at equal temperatures, are placed over flames of gas burners of equal size, it will be found that the water will require nearly 30 min. to reach the same temperature as that reached by the mercury in 1 min. The water is therefore said to have a greater capacity for heat than has mercury. In order to express the idea of relative heat capacities, the term **specific heat** is employed. This may be defined as the ratio of the quantity of heat that must be added to a given mass of a substance in order to raise its temperature 1° as compared with the quantity of heat that is required to raise the temperature of an equal mass of water through 1°. The measurement of these values is usually made under given conditions of volume and pressure. Since specific heat is a ratio of the number of heat units required in each case, it makes no difference whether the actual amount of heat is measured in terms of gram-calories, kilogram-calories, or British thermal units, so long as the heat is measured with reference to equal weights or masses of the

substances being tested. Furthermore, since specific heat is a ratio, it makes no difference whether the elevation in temperature is measured in degrees centigrade, Fahrenheit, or Reaumur, provided that the same kind of degree is employed in making both tests. The specific heat of a few solids and liquids is given in Table XVI.

TABLE XVI.—SPECIFIC HEAT OF SOME LIQUIDS AND SOLIDS[1]

Substance	Specific heat	Substance	Specific heat
Aluminum	0.2111	Mercury	0.0332
Alcohol	0.5480	Nickel	0.1078
Copper	0.0923	Platinum	0.0316
Ether	0.5290	Tin	0.0545
Gold	0.0316	Water	1.0000
Glycerin	0.0316	Zinc	0.0927

[1] Selected from a table appearing in "The Encyclopedia Americana," 1940, Vol. 14, p. 45.

Water is remarkable in that it has the greatest specific heat of all ordinary substances. It can be seen from the value in Table XVI that it would take approximately eleven times as much heat energy to raise the temperature of 1 lb. of water 1° as would be required for 1 lb. of copper. Vast bodies of water such as the oceans and large lakes play an important role in moderating the extremes of temperature because of the enormous heat capacity of water. During the summer months great quantities of heat are absorbed which are given off slowly during the winter. This fact helps to explain why the temperature on some of the smaller islands of the ocean does not vary more than 10°F. during the entire year.

THE GENERATION OF HEAT

Heat, light, electricity, and motion are only different forms of energy that affect molecules of matter. Each of these forms of energy is capable of transformation, within certain limitations, into any other form, and the change that is produced is **reversible.** It should not be assumed that these conversions are quantitative in nature in all cases, for, in certain instances, the transfer of energy is made with varying degrees of efficiency; but the inter-

changeability of these four forms of energy may be easily demonstrated. In the generation of heat, we are concerned primarily with the conversion of light, electricity, or motion into heat energy. The principal ways in which heat may be generated involve mechanical, electrical, or chemical processes.

Friction.—The fact that friction, a form of mechanical energy, generates heat is common knowledge. The method of primitive peoples for kindling fire by rubbing two sticks together and the use of the flint and steel for the same purpose are examples of the production of heat by friction. The fact that friction generates heat is more often a disadvantage than an advantage, particularly in this modern, mechanized world in which we live. Constant attention must be given to the problem of overcoming this effect by lubrication of the moving parts of machinery. Although friction is recognized as a source of heat, almost no application of this method of heat generation has been made available for practical use.

Light.—Although light energy is of no practical importance as a source of heat, it is a well-known fact that its production is always accompanied by the elaboration of some heat. Here again, this is not without its disadvantages. A familiar example of this is found in the slide and motion-picture projectors, in which special cooling devices, such as motor-driven fans, are used to dissipate the heat given off by the strong source of light used in these instruments in order to prevent damage to the slides or films. Although considerable progress has been made in this direction, scientists are still concerned with the problem of the complete conversion of other forms of energy into light, with the production of the so-called "cold light" as their goal.

Electricity.—The use of electricity as a source of heat is very general and is familiar to everyone. The most common method for converting electrical energy into heat energy is to pass an electric current through a substance that is a relatively poor conductor of electricity or that offers resistance to its passage. Under these conditions, the molecular friction that the resistance sets up is manifested by the production of heat. In the past it was customary to classify materials as conductors and non-conductors, but these terms have gradually fallen into disuse, since the properties indicated by them are relative rather than

absolute. The practice now is to use the terms **resistance** and **conductivity** to describe these properties of matter.

Combustion.—By far the most widely used method for generating heat is by chemical means, or by combustion of substances known as **fuels.** The materials used as fuels are rich in carbon and hydrogen in combined form; and, upon complete oxidation in the presence of air or oxygen, these elements are converted into the gases, carbon dioxide, and water vapor. The heat energy generated is known as the **heat of combustion.** The fuels may be classified according to their physical forms as solid, liquid, and gaseous.

Solid Fuels.—Among the solid fuels commonly used are wood, coal, coke, charcoal, and peat. Although these are widely used for the purposes of cooking, domestic heating, and power production in industry, they find little use in pharmaceutical processes involving the application of heat.

Liquid Fuels.—The liquid fuels in common use include alcohol (both grain alcohol and wood alcohol, or mixtures of these) and the petroleum products, like gasoline, petroleum benzin, and products such as some of the heavier fractions obtained by fractional distillation of crude petroleum oil. Within recent years the use of the crude petroleum itself, especially for domestic heating and power production, has become general. The liquid fuels employed in pharmaceutical operations are restricted to alcohol and, to a lesser extent, gasoline and petroleum benzin.

Gaseous Fuels.—The principal gaseous fuels are manufactured illuminating gas (which may be of several types, such as coal gas, coke oven gas, water gas, and flue gas), natural gas, propane, butane, Pyrofax, and acetylene gas. The latter consists of the unsaturated hydrocarbon, acetylene (C_2H_2), and is usually prepared by the action of water on calcium carbide (CaC_2). Because of the convenience with which the flow of gases may be regulated and controlled, fuels of this type are used almost exclusively in pharmaceutical operations requiring the application of heat.

Gas Burners.—If illuminating gas is ignited as it is emitted from a tube, it burns with a luminous flame. A cold surface held above the flame, such as the bottom of a porcelain evaporating dish, will soon show a deposit of soot, or carbon. The

color imparted to the flame is the result of incomplete combustion, the minute particles of carbon that are formed becoming incandescent in the flame. This occurs because an insufficient supply of oxygen is available to permit complete oxidation of the carbon to carbon dioxide, which is a colorless gas.

Bunsen Burners.—In order to obtain a nonluminous flame and at the same time increase the thermal efficiency of the combustion process, the principle perfected by Robert Bunsen, the German chemist, has been adopted, and the operation of most devices used for burning gaseous fuels depends upon this principle. The

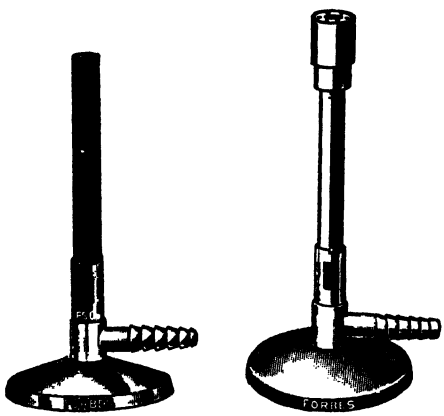
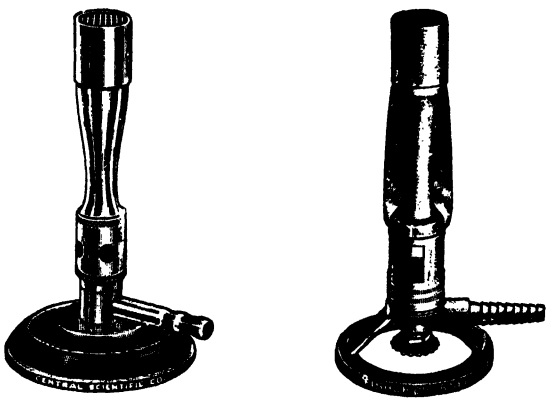


FIG. 58.—Bunsen burners.

burner developed by Bunsen provides for the admission of air at the base of a mixing tube, the mixture being ignited at the upper end of the tube. The supply of air may be regulated to adjust for differences in the composition of gaseous fuels and to compensate for differences in the rate of flow of the fuel. Under these conditions a nonluminous flame is obtained, and the amount of heat produced is much greater than that of the luminous flame, since a more complete combustion of the gas is obtained.

The ordinary bunsen burner produces a double cone-shaped flame, with the greatest intensity of heat at the tip of the inner cone. In the operation of the burner, a tendency for the flame to strike back, or flash back, is noticed, which means that, instead of burning at the end of the burner, the flame ignites the gas at the gas orifice at the base of the mixing tube. This

behavior is usually noted if the adjustment of the air vents is relatively wide as the flow of gas is turned down to a low rate. This can usually be prevented by partly closing the air vents before reducing the flow of gas. Certain improvements have been made in the design of burners in order to increase their efficiency. The burner on the right in Fig. 58 is provided with a special shield, or flame retainer, designed for use where natural gas is to be used as the fuel. This serves to overcome the tendency that the flame produced by this fuel has to blow out, especially when the flame is reduced to a low level. Other



Meker. Fisher.

FIG. 59.—High-temperature burners.

refinements that have been added include needle valve controls for both the gas and the air admitted to the burner.

High-temperature Burners.—To overcome the tendency of the ordinary bunsen burner to flash back and at the same time increase the efficiency of the burner and permit higher temperatures to be attained, special types of burner have been developed employing the principle of the Davy safety lamp, which is used in mining. When a wire gauze or screen is heated by a flame, the wire of the gauze, being an excellent conductor, tends to dissipate the heat rapidly, with the result that the flame is actually cooled. Under these conditions, it is impossible for the flame to pass through the gauze and ignite the inflammable vapors on the other side. At the same time the wire screen breaks up the flame into numerous cones, which extend only a short distance

above the screen. This provides a flat zone in which extremely high temperatures are reached, in the neighborhood of 1800°C., which is considerably higher than the highest temperature attained in any part of the flame of the ordinary bunsen burner.

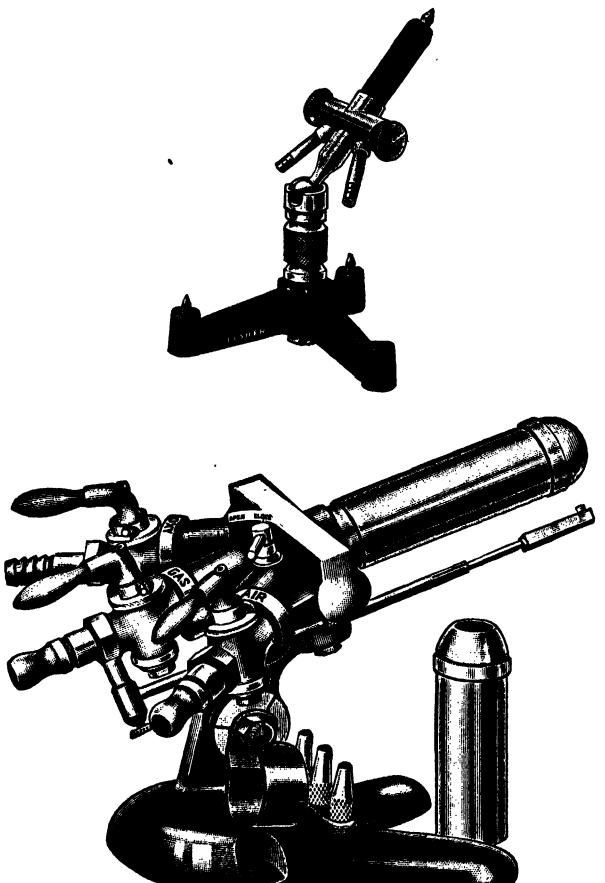


FIG. 60.—Blast lamps.

Blast Burners.—For certain types of work, such as ignitions, fusions, glass blowing, and welding, still higher temperatures are required. The devices used for this purpose are variously known as blast burners, blast lamps, blowtorches, and blast furnaces. The principle involved is the same as that of the bunsen burner,

except that the process of combustion is accelerated by supplying compressed air to the burner. Still higher temperatures may be attained if both the fuel gas and the air are under increased pressure. The maximum rate of combustion is attained, with a corresponding increase in temperature, if compressed oxygen is substituted for air. Since the air normally contains only about 21 per cent by volume of oxygen and oxygen is the only constituent of the air that supports combustion, the increase in the combustion rate is very great. Thus the oxyacetylene torch is capable of fusing thick layers of steel plate almost upon contact.

THE REGULATION OF HEAT

In many of the pharmaceutical operations requiring the application of heat, suitable means of distributing, limiting, or regulating the heat must be provided, since almost all medicinal substances may undergo chemical changes or be completely destroyed if exposed to high temperatures. Some of the devices employed serve only to give a more uniform distribution of heat, without in any way limiting the temperature, while others fulfill both functions.

The Wire Gauze.—Since the heat of the bunsen burner is concentrated, especially at the tip of the inner cone of the flame, there is need for distributing this heat more or less uniformly in the heating of materials contained in porcelain or glass containers. Otherwise there is some danger of breakage of the container due to the very rapid increase in temperature, and the further risk of overheating the material locally in the zone immediately adjacent to the flame. The wire gauze is commonly used for the purpose of attaining uniform heat distribution. It is generally accepted as a standard practice that dishes, beakers, flasks, etc., are not to be heated in the direct flame of the burner, except in special cases, such as ignitions and incinerations. The wire gauze does not limit the temperature that will be reached, but it is effective in distributing the heat more or less uniformly. This is explained by the fact that the wire is an excellent conductor and rapidly transmits the heat away from the point of contact with the flame. Wire gauzes are made of iron wire, of special alloys such as Nichrome, Monel metal, and Chromel, of brass, and of copper. Copper gauze is perhaps the least

desirable, because of the ease with which it is oxidized upon being heated. Iron wire gauze is somewhat more resistant, but upon long heating tends to become partly oxidized and brittle. On the other hand, gauzes made of Nichrome, Monel metal, and Chromel wire are especially heat-resistant and show little tendency to become oxidized, even after prolonged use.

The Sand Bath.—Another convenient means of distributing heat is the sand bath. This consists of a container, usually made of sheet iron, partly filled with sand, which is to be packed around the utensil to be heated. Just as in the use of the wire gauze, the sand bath in no way limits the temperature that may be reached. However, sand is a relatively poor conductor of heat as compared with wire gauze, and because of this difference

FIG. 61.—Sand baths.

the sand bath is especially useful in preventing rapid fluctuations in temperature, such as may occur in heating with the wire gauze. The sand transmits heat much more slowly and as a result tends to hold the heat longer. A wire gauze becomes cooled to room temperature rather quickly after the flame is withdrawn, but the sand bath retains considerable heat for an extended period. This effect is not altogether due to the difference in these two materials in their ability to conduct heat but is partly accounted for by the fact that the quantity of sand used in the bath greatly exceeds the quantity of metal contained in the wire gauze. For this reason, the sand bath is commonly preferred where heating at comparatively high temperatures is required, especially where it is desirable for the temperature to remain more or less uniform.

The Water Bath.—One of the most convenient and widely used methods of providing for the distribution of heat and at the same time limiting the temperature is the water bath. Since the boiling point of water at an atmospheric pressure corresponding to 760 mm. of mercury is 100°C. (212°F.), it follows that the contents of a beaker or dish placed on a water bath

cannot exceed this temperature so long as any water remains in the water bath. As a matter of fact, the maximum temperature reached by the liquid being heated on the water bath is found to be considerably below the boiling point of water, depending upon the amount of heat lost by radiation, but usually approaches the range of 85 to 95°C. The latter temperature is usually attained only if the dish or beaker is actually in contact with the boiling water. This use of the water bath is sometimes known as indirect heating and has been employed for a long time. It is

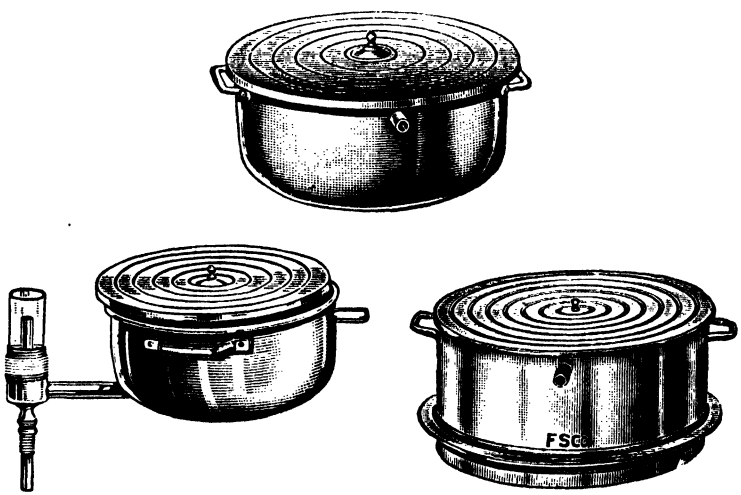


FIG. 62.—Water baths.

of some historic interest to note that, according to D. Lloyd Howard,[1] a patent was issued in England in 1692 to Anthony Smith for the idea of evaporating liquors by means of the heat from other boiling liquids. The similarity between the water bath and the familiar double boiler used in the kitchen is at once apparent.

Various utensils may be adapted for use as a water bath, such as a large beaker or evaporating dish. For greater convenience, a container especially designed for the purpose is commonly used. This usually is a vessel made of copper, ordinarily with a rounded

[1] A. O. BENTLEY. "A Text-book of Pharmaceutics," Baillière, Tindall & Cox, London, 4th ed., 1937, p. 75.

bottom, and provided with a cover consisting of a series of concentric rings for convenience in adjusting to the dimensions of containers of various sizes that are to be placed on the water bath. One of the points to be remembered in the use of the ordinary water bath is the fact that in due time all the water will be boiled away unless the supply is replenished from time to time. For this reason a constant-level device is a useful accessory. This consists of a vertical tube connected by means of a side-arm tube to the water bath near its base. The vertical tube contains a smaller overflow tube, which is adjustable as to its height, automatically controlling the level of the water in the bath. A small stream of water is kept continually flowing into the larger vertical tube, and the excess is drained off through the overflow tube.

Other Liquid Baths.—Occasionally it is desirable for certain substances to be heated to temperatures considerably higher than the boiling point of water, some limitation of the temperature being required at the same time in order to protect the substance being heated. In such cases, other liquids are commonly used to replace the water in the bath. For temperatures only slightly higher, such liquids as toluene ($C_6H_5CH_3$) (b.p. approximately 108°C.) or xylene ($C_6H_4(CH_3)_2$) (b.p. approximately 140°C.) may be used. For still higher temperatures, such liquids as the vegetable oils (cottonseed oil, expressed oil of almonds, corn oil, sesame oil, peanut oil, etc.) or glycerin may be used. Vegetable oils may be used for temperatures up to approximately 260°C.; at this point, decomposition sets in, with the liberation of the irritating vapors of acrolein. Glycerin may also be used, but again at temperatures not exceeding 250°C., since this compound also develops the vapors of acrolein at approximately this temperature. Some of the artificial fats obtained by hydrogenation of cottonseed oil and other vegetable oils, such as Crisco or Spry, may be used with somewhat better results since these substances show little tendency to decompose even upon long heating. For still higher temperature ranges, the higher distilling fractions obtained from crude petroleum, such as mineral oil, may be used. Since these fractions consist largely of saturated hydrocarbons, they withstand the effect of heat, even for considerable periods of time, without serious decomposition.

Petrolatum, paraffin, beeswax, and other natural waxes are sometimes used. For still higher temperatures a number of fusible metallic alloys have been developed that are extremely useful. These are solid at ordinary temperatures but become liquid at temperatures of 100°C. or lower. The more commonly used alloys of this type are given in Table XVII. It should be remembered that the chief effect of a bath in which a fusible metallic alloy is used is to distribute the heat and guard against fluctuations in temperature. For the most part, the boiling points of these alloys are so high that they exert no limiting effect on the maximum temperature. When these substances are used, the control of temperature is dependent upon the source of heat and the way in which it is regulated.

TABLE XVII.—FUSIBLE METALLIC ALLOYS[1]

Name	Composition, per cent				Melting point, °C.
	Bismuth	Lead	Tin	Cadmium	
D'Arcet's alloy	50	25	25	....	93.7
Lichtenberg's alloy	50	30	20	....	91.6
Lipowitz's alloy	50	27	13	10	60
Newton's alloy	50	31	19	....	94.5
Rose's alloy	50	28	22	....	100
Wood's metal	50	25	12.5	12.5	71

[1] Selected from a table given in Webster's New International Dictionary of the English Language, 2d ed., 1939, p. 1022.

The Constant-temperature Bath.—For certain processes, assays, and tests, it is frequently necessary to maintain an approximately uniform temperature (usually below 100°C.) for extended periods of time. The constant-temperature bath is used for this purpose. In its simplest form, the necessary apparatus includes a thermometer; a thermostat, or temperature-regulating device; a mechanical stirring device in order to ensure uniform distribution of the heat; and a source of heat, which is automatically controlled by the thermostat. The operation of the thermostat is based upon the expansion and contraction of certain organic liquids, or mercury, which serve to turn the supply

of gas on or off or to open and close the electrical circuit of a heating element, as may be required, in order to maintain a uniform temperature. Certain of these devices may be adjusted to a remarkable degree of accuracy. One manufacturer claims that the constant-temperature bath of his design, employing an electric heating unit, is capable of maintaining a predetermined

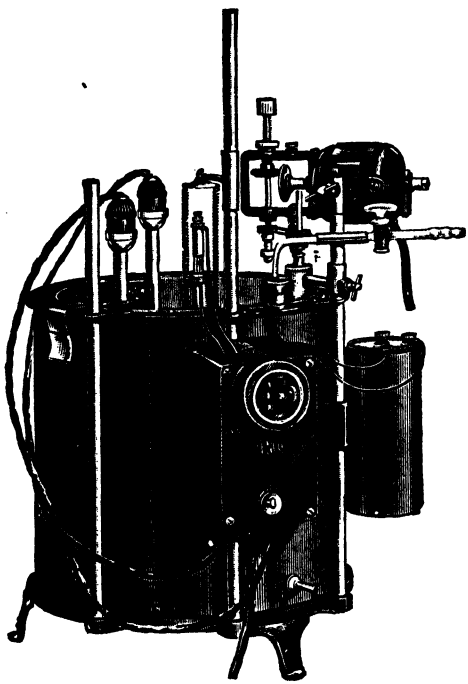


FIG. 63.—Constant-temperature bath.

temperature which does not vary more than 0.02 of a centigrade degree.

The Steam Bath.—For greater convenience in the application of heat, particularly in large-scale operations, the steam bath is frequently substituted for the water bath. The greater convenience is due largely to the fact that the steam may be distributed to various parts of the laboratory as required by means of pipes from a central generator or boiler and that this method is a more efficient process of transmitting heat. This greater

efficiency is explained by the fact that although the temperature of steam, at a pressure of 760 mm. of mercury, is the same as that of boiling water (100°C.), the heat capacity of steam is much greater. This is due to what is sometimes called the "latent" heat of steam. If water is heated up to its boiling point, it shows a progressive rise in temperature, as the heating continues, until ebullition actually occurs. From this point on, the addition of heat energy has no apparent effect in elevating the temperature. This energy is not lost, however, as the term *latent* implies, but is consumed in driving the molecules of water farther apart so that the liquid phase changes to a vapor.

The effect of this additional heat energy contained in steam may be illustrated as follows: If equal weights of water at 0°C. and at 100°C. are mixed, the temperature of the resulting mixture will be 50°C., the average of the two extremes of temperature. If, on the other hand, equal weights of water at 0°C. and steam at 100°C. are mixed, the water will be brought to a temperature of 100°C. The additional heat energy contained in steam at atmospheric pressure, commonly known as the latent heat of steam or of vaporization, becomes available as sensible heat as the vapor condenses to the liquid phase. Careful measurements have shown that the latent heat of steam is approximately 537 calories. The amount of heat necessary to elevate the temperature of 1 Gm. of water to the temperature of 100°C., its boiling point, is 100 cal. One gram of steam at the same temperature therefore contains 5.37 times as much heat energy. This difference in heat value explains the greater efficiency of steam over boiling water as a means of transmitting heat.

The efficiency of steam as a source of heat may be still further increased by increasing the pressure. When water is heated under ordinary atmospheric pressure, it boils at that temperature at which its vapor pressure just exceeds the pressure of the atmosphere, namely, at 100°C. if the pressure corresponds to 760 mm. of mercury. If, however, the water is boiled in a closed container, such as a boiler, the pressure produced by its own vapor prevents the liquid from boiling until a higher temperature is reached and the temperature of the steam which is produced under these conditions will be correspondingly higher. The normal atmospheric pressure approximates 14.7 lb. per sq. in.

Accordingly, if water is brought to a boil at pressures lower than this value, the temperature of the steam will be correspondingly

TABLE XVIII.—STEAM TEMPERATURES AT VARIOUS PRESSURES[1]

Pressure, lb. per sq. in.	Temperature, °C.
5	109
10	116
15	120
25	130
30	135
80	163

[1] BENTLEY. *Op. cit.*, p. 86. The pressures shown in this table are expressed in terms of gauge pressures, or pressures above atmospheric pressure.

lower than 100°C. On the other hand, if the pressure is greater than 14.7 lb. per sq. in., the temperature of the steam is correspondingly greater than 100°C. Some idea of the effect of increased pressure on the temperature of steam may be seen in Table XVIII.

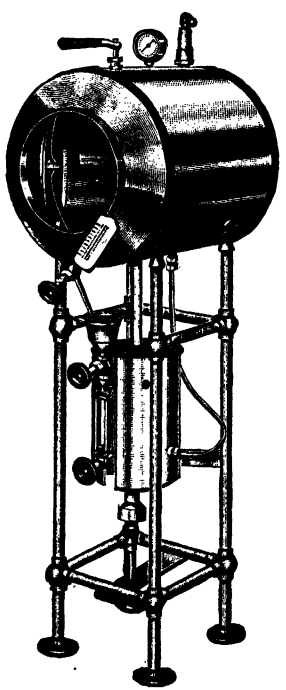
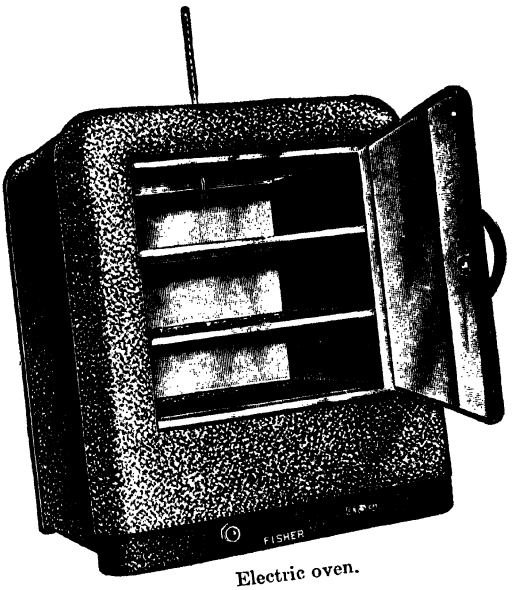
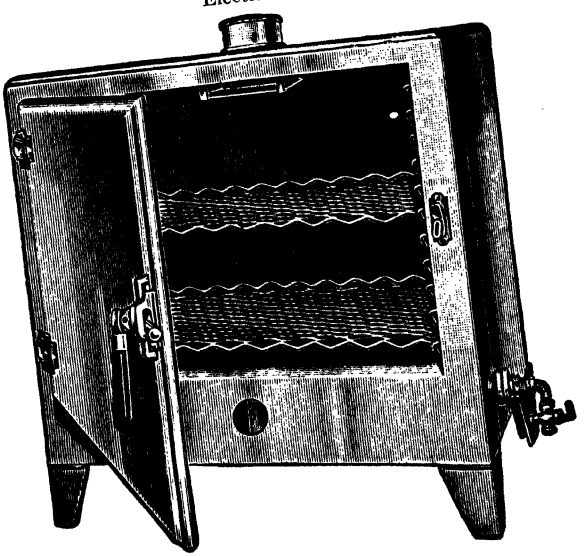


FIG. 64.—Steam sterilizer.

Steam Sterilizers.—A special application of steam under pressure is that of sterilization (see Chap. XII, page 388) of solutions of medicinal substances which would be destroyed by the higher temperatures necessary to effect sterilization by dry heat. Advantage is taken of the fact that steam under pressure shows an increase in temperature. The steam sterilizer, commonly called the autoclave, consists essentially of a boiler or other source for steam generation under pressure, connected to a larger chamber capable of withstanding pressure and provided with a thermometer and a safety valve, which may be adjusted for different pressures. The use of steam under pressure is described as one of several methods of sterilization under process *C*, page 616, of the Pharmacopoeia XII. The recommendations for the steam pressures to be employed and the necessary periods of time required for adequate



Electric oven.



Hot-air steriliser.

FIG. 65.—Air baths.

sterilization, together with the corresponding temperatures attained, as given therein are as follows: 10 lb. pressure (115.5°C.) for 30 min., 15 lb. pressure (121.5°C.) for 20 min., 20 lb. pressure (126.5°C.) for 15 min.

Air Baths.—An indirect method of heating, depending upon the transfer of heat by the use of heated air, which effects the transfer principally by convection and radiation, is represented by the air bath. The devices used for this purpose are known by a variety of names, such as drying ovens, drying closets, incubators, or hot-air sterilizers. Some of these devices are provided with thermostatic control of the temperature. In other cases the only means of controlling temperature is by the regulation of the source of heat. In bacteriological work it is required that the cultural media used for the growth and propagation of bacteria shall be maintained at temperatures approximating body temperature. The incubators used for this purpose are provided with thermostatic control and are usually operated at approximately 37°C. For certain pharmaceutical manufacturing operations, such as the granulation of effervescent salts or the preparation of granulated material to be compressed into tablets, large drying ovens are provided, which maintain temperatures in the region of 100°C. For the sterilization of glassware and other apparatus that is not affected by high temperatures, hot-air sterilizers are available, usually employing gas heat. Although dry-heat sterilization is ordinarily conducted at a temperature range of 160 to 190°C., some of the hot-air sterilizers of this type are capable of reaching a temperature as high as 400°C.

STUDY QUESTIONS

1. Explain the phlogiston theory of heat.
2. What was the caloric theory of heat?
3. Explain fully the modern conception of heat.
4. What practical application is made of the fact that the coefficients of linear expansion are almost identical for platinum and glass?
5. For what special uses is Invar steel particularly well adapted because of its small coefficient of linear expansion?
6. What is the first law of thermodynamics?
7. Name and define the ways in which heat is transmitted.
8. How is the intensity of heat measured?
9. How is the quantity of heat measured?

10. How did Fahrenheit determine the fixed points of reference that he used to develop his thermometer scale?

11. Explain how the absolute zero was determined to be −273°C.

12. How does the Anschütz thermometer differ in construction from other types of thermometer?

13. What are the special characteristics and uses of the differential thermometer?

14 What detail of construction of the clinical thermometer permits it to function as a self-registering thermometer?

15. Define (*a*) the calorie; (*b*) the British thermal unit.

16. For what purpose is the calorimeter used?

17. Define specific heat.

18. What is noteworthy concerning the specific heat of water as compared with the corresponding values for other liquids and solids?

19. What are the principal forms of energy that serve as sources of heat?

20. Explain the principle of the bunsen burner.

21. Explain why higher temperatures may be reached with the blast burner than with the ordinary bunsen burner.

22. What functions are performed by (*a*) the wire gauze; (*b*) the sand bath?

23. Explain how the water bath regulates heat.

24. What liquid should you recommend for use in a bath intended to limit the temperature to approximately 135°C.?

25. Explain fully the advantages of the steam bath over the water bath as a source of heat.

26. What is the effect of pressure upon the temperature of steam?

27. What is the autoclave, and for what purpose is it used?

28. What pressures, temperatures, and periods of time of exposure are recommended as essential to adequate sterilization by the use of steam under pressure?

29. What temperature is ordinarily maintained in incubators used in bacteriological work?

30. What are the usual temperature ranges employed in dry-heat sterilization?

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CHAPTER X

APPLICATIONS OF AND PROCESSES INVOLVING HEAT

Having considered the theory of heat and its generation and control in the preceding chapter, we now turn our attention to the applications of heat to pharmaceutical operations and the study of those processes in which physical or chemical changes are produced by heat energy. These processes are to be discussed in some detail in this chapter and Chap. XI. The specific processes to be considered include the following: fusion, evaporation, ebullition, desiccation, exsiccation, ignition, calcination, deflagration, carbonization, incineration, torrefaction, refrigeration, distillation, and sublimation.

Fusion.—As explained in Chap. IX, solid substances tend to retain their solid state because of the mutual attraction, or cohesion, of the molecules, this force being augmented slightly by the atmospheric pressure. As heat is applied to the substance, the molecular vibrations are increased in amplitude, producing a corresponding expansion in the solid. If the application of heat is continued long enough, a certain temperature is reached, which is characteristic for each substance, at which the solid material changes to the liquid state. This change is known as **fusion** or **melting.** If the resulting liquid is then cooled slightly, the reverse process, known as **congelation** or **freezing,** occurs and the liquid again becomes solid. The transition temperatures for these changes, known as the **melting point** and the **congealing point,** respectively, are important physical properties, since, for a pure chemical substance, these values are constant at a given pressure. As a matter of fact, minor differences in atmospheric pressure have so slight an influence upon melting points and congealing points that corrections for this effect are usually ignored. The constant melting point holds true for pure substances only, an impure substance always showing a lower value. Consequently, this physical property is a valuable means of identification of pure substances and also serves as a clue in the detection of adulteration of solid substances.

The changes in physical form produced by heat may be illustrated by the behavior of ice. As heat is applied, the ice begins to liquefy, or melt. A thermometer placed in the mixture of ice and water will show a temperature of 0°C. (32°F.) provided that the mixture is well stirred, and this temperature will remain constant until the last portion of ice has disappeared, even though heat is being applied continually. This occurs because, at the point of fusion, all the heat energy is consumed in forcing the molecules apart as the solid is changed to a liquid. The heat energy required for this purpose is known as the **heat of fusion** or the **latent heat of fusion.** Careful determinations have shown that the amount of heat energy required to convert 1 Gm. of ice into water at 0°C. is 79.7 cal.

If the water resulting from the fusion of the ice is heated still further, a more or less uniform increase in temperature will be noted until a temperature of 100°C. (212°F.) is reached, where again the temperature becomes constant, and boiling of the liquid begins. As explained in the discussion of steam baths in Chap. IX, at this point the additional heat energy is absorbed and utilized in forcing the molecules of the liquid still farther apart to form the vapor phase. The heat of vaporization of water (the amount of heat required to change 1 Gm. of water at 100°C. into water vapor of the same temperature) has been determined as 537 cal.

Melting-point Determinations. SOLIDS OF CLASS I.—The Pharmacopoeia defines the melting points, or ranges, of solids as "those points or ranges of temperature at which or within which they are observed to melt" when treated in accordance with the directions given for one of the prescribed tests for the determination of melting points. For detailed information on melting-point determinations, the official monograph on Melting Points that appears in the twelfth revision of the Pharmacopoeia, page 595, should be consulted. Three distinct classes of solid substances are listed, with separate procedures outlined for each class. The classification is as follows:

Class I. Materials readily reduced to a powder.

Class II. Materials not readily reduced to a powder, such as fats, fatty acids, paraffin, and waxes.

Class III. Petrolatum.

For materials of Class I, which includes most chemical compounds of known composition and represents by far the most numerous of the three classes listed, the apparatus required for the test consists of a round-bottom glass tube, 30 to 40 mm. internal diameter, and about 10 cm. long; a stirring device, which may be made by bending a glass rod in the proper shape; a standard thermometer of Type I or Type II, as described on page 622 of the Pharmacopoeia; an auxiliary thermometer; and a capillary glass tube, about 6 cm. long and 0.8 to 1.2 mm. internal diameter, the walls being 0.2 to 0.3 mm. thick and the tube being closed at one end.

The material to be tested is reduced to a very fine powder and, unless otherwise directed, is rendered anhydrous by suitable drying, either over sulfuric acid for 24 hr. or by heating at the specified temperature for the prescribed period of time. A sufficient amount of the material to be tested is placed in the tube to form a column 2.5 to 3.5 mm. in height. The capillary tube is then attached to the thermometer, either by wetting the surface of each with the liquid to be used in the heating bath and placing the tube alongside the thermometer, whereupon it will be held in place by capillary attraction, or by means of a platinum wire, in such a position that the sample is adjacent to the bulb of the thermometer. The thermometer is then adjusted so that the upper end of the bulb is 2 to 3 cm. below the level of the liquid in the heating bath. The auxiliary thermometer is then placed in position, forming an angle of approximately 45 deg. with the main thermometer, the bulb being located as close as possible to the stem of the main thermometer, and at a point halfway between the upper surface of the heating bath and the graduation of the main thermometer, representing the anticipated melting point of the sample. In order to prevent heat from the burner or currents of colder air from affecting the reading of the auxiliary thermometer, the use of a shield made of stiff paper is recommended.

The bath is heated by means of a bunsen burner until a temperature is reached that is about thirty degrees below the supposed melting point; at this point the rate of heating is decreased to about three degrees per minute until the sample begins to melt; from this time on, the rate of increase in tempera-

ture is reduced to about one-half degree per minute until the sample has completely melted. The temperature at which the column of the sample is observed to collapse against the side of the tube is regarded as the beginning of melting.

The reasons for the use of the auxiliary thermometer and the emergent stem correction were given briefly in the discussion of the Anschütz thermometer in Chap. IX. It was pointed out there that the need for this correction arises from the fact that the heat transmitted to the main thermometer stem by conduction and convection causes the glass tube of the thermometer to expand, which results in distortion and interferes with the accuracy of the thermometer scale. The emergent stem correction is calculated according to the following formula:

$$\text{Correction} = 0.00015 \times N(T - t)$$

in which N represents the number of scale divisions (in degrees) of the emergent stem from the level of the heating bath to the temperature attained at the end of melting, T is the temperature at the end of melting, and t is the temperature reading of the auxiliary thermometer. As mentioned previously, in Chap. IX, in making routine determinations of melting points where extreme accuracy is of minor importance, the necessity of emergent stem corrections may be avoided by using a thermometer of the Anschütz type.

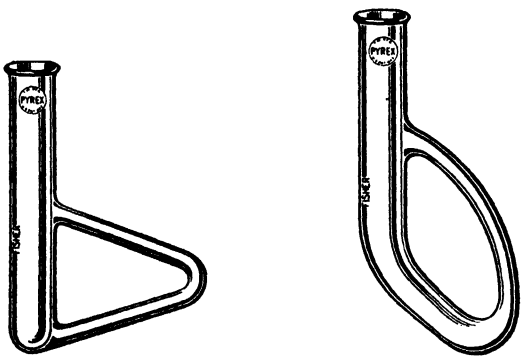
The following suggestions regarding liquids to be used in the heating baths for melting-point determinations are given in the Pharmacopoeia:

For temperatures up to 200°C., a purified, concentrated sulfuric acid is a suitable bath. For higher temperatures, up to about 350°C., a pure grade of cottonseed oil (almost colorless) will serve for a limited number of determinations. Other, though less desirable, substitutes for sulfuric acid for use at high temperature are: (1) a pure grade of paraffin which has been freshly distilled; (2) clean, white, hydrogenated cottonseed oil. A very satisfactory bath is prepared by cautiously boiling together, for 5 to 10 minutes under a hood, a mixture of 70 parts of sulfuric acid and 30 parts of potassium sulfate, stirring constantly until the potassium sulfate is completely dissolved.

A less cumbersome and equally satisfactory substitute for the tube and stirring device recommended by the Pharmacopoeia for

determining the melting points of substances of Class I is represented by the Thiele melting-point tube shown in Fig. 66. This consists of a wide tube, provided with a bent side arm, one end of which is attached to the tube near its lower end, the other end of the side arm being sealed into the side wall of the tube at a higher elevation.

The tube is filled with the liquid selected for use as the heating bath to a level slightly above the upper opening of the side arm. As heat from the burner is applied at the elbow of the side arm, the resulting expansion of the liquid sets convection currents into circulation, which tend to distribute the heat more or less uni-



Thiele. Thiele-Dennis.

FIG. 66.—Melting-point tubes.

formly throughout the bath. The use of stirring devices is eliminated, which enables the operator to give his undivided attention to the behavior of the sample and the observation of the temperature reading as the sample begins to melt.

Special melting-point apparatus of various types have been suggested for use in determining the melting points of crystalline substances. Most of these have been designed for the purpose of reducing the time necessary to complete the determination and at the same time maintaining a high degree of accuracy. One of the devices that has been recommended is known as the Fisher-Johns melting-point apparatus. This apparatus was developed in accordance with the suggestions of Dr. I. B. Johns of Iowa State College. The sample to be tested is placed between cover glasses on an aluminum stage, which is heated by passing an

electrical current through a controlled resistance. A magnifying lens is mounted above the sample, which facilitates the detection of the actual point at which melting occurs. A thermometer is mounted horizontally, with the bulb located immediately below the stage. The advantage claimed for the use of this apparatus is the elimination of the need for sulfuric acid or other heating baths and of stirring devices. The rate of increase of temperature may be accurately controlled.

A somewhat more elaborate apparatus is that known as the Dennis melting-point apparatus, manufactured by the Parr

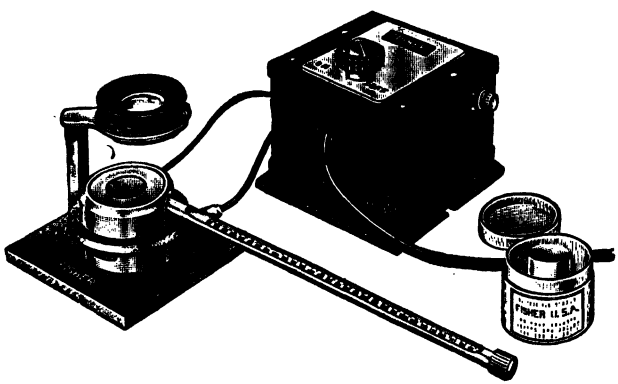


FIG. 67.—Fisher-Johns melting-point apparatus.

Instrument Company of Moline, Ill. The advantages claimed for the use of this device are the ease of operation, the decreased time required for the determination, and the high degree of accuracy attained. This instrument was developed by Dr. L. M. Dennis and his associates in the chemistry department of Cornell University, and is described in detail in a paper by Dr. Dennis.[1] The temperature measurements are made by the use of a copper-constantan thermocouple in conjunction with a potentiometer. The apparatus consists essentially of a bar of pure copper, which is provided with an electrical heating coil at one end and cooling fins for the radiation of heat at the other. A constantan wire is attached to a traveling arm, which may be moved along the full length of the bar. Copper and constantan leads from the bar and the wire are provided for connection with the potentiometer.

[1] L. M. DENNIS. *J. Am. Chem. Soc.* **52**, 3128 (1930).

A bimetallic couple is formed when the wire comes in contact with the bar, and the electromotive force which is produced is proportional to the temperature of the bar at that particular point of contact, as indicated by the potentiometer.

The material to be tested, if in the form of large crystals, is reduced to a fine powder and sprinkled lightly on the top of the copper bar. Only a small amount of sample is required, and this is arranged in the form of a train of powder two or three inches in length. The heating circuit is turned on, and the temperature of the bar is allowed to rise until the melting point of the material is reached. Since the heat is applied at one end of the bar and the radiation fins at the other end produce a

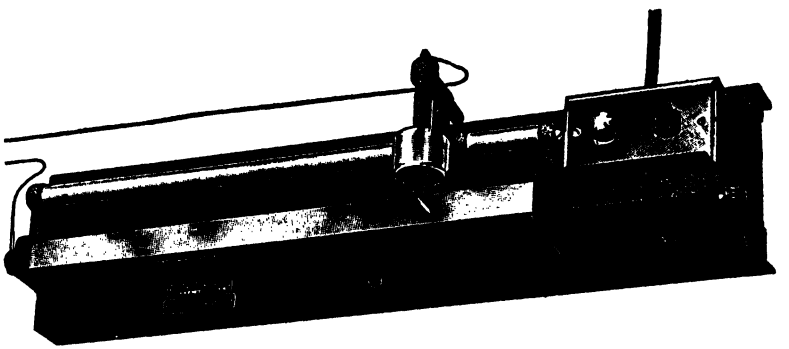


FIG. 68.—Dennis melting-point apparatus.

cooling effect, this permits a temperature gradient to be set up that results in a sharp boundary between the molten and the solid material. The contact of the constantan wire with the copper bar is placed slightly ahead of the advancing line of fusion as the temperature of the bar increases. The reading of the potentiometer is taken at the instant when the line of demarcation is just opposite the contact of the constantan wire. By changing the adjustment of the contact to more advanced positions, a number of melting-point readings may be taken with the same sample.

The manufacturer of this apparatus claims that a complete determination may be made within 5 min. or less and that check determinations may be made within 30 sec. All errors due to thermometer lag or the necessity for moving the thermometer

before it can be read are eliminated since the bimetallic couple is made at the exact point on the bar where the melting occurs. It is further claimed that the operation is so simple and direct that accurate results may be obtained, even by inexperienced operators.

SOLIDS OF CLASS II.—Special provisions are made for materials not readily reduced to a powder, such as fats, fatty acids, paraffin, and waxes. It has been found that, when materials of this type are tested after having been recently fused, sharp melting points are not obtained. If the freshly melted material is subjected to refrigeration prior to testing, this error is avoided. The directions as given in the Pharmacopoeia provide that the material shall first be melted at the lowest temperature possible and drawn up in a capillary tube open at both ends to a height of approximately 10 mm. The charged tube is then cooled at 10°C., or lower, for 24 hr. or in direct contact with ice for at least 2 hr. The procedure is the same as that followed for solids of Class I, except that, within 5° of the anticipated melting point, the rate of increase in temperature is restricted to about one-half degree per minute. Since most of the substances of this class have relatively low melting points, water is ordinarily used as the heating bath. The temperature at which the material is observed to rise in the tube is taken as the melting point.

SOLIDS OF CLASS III.—Because petrolatum is a mixture of hydrocarbons rather than a pure substance, its behavior upon fusion renders necessary a special procedure. The method described in the Pharmacopoeia under the heading Procedure for Testing Materials of Class III appears for the first time in the twelfth revision.

The procedure is as follows: The sample of petrolatum is melted slowly, with stirring, and the heat continued until the temperature reaches 90 to 92°C. The source of heat is then removed, and the molten material is allowed to cool to a temperature 8 to 10° above the anticipated melting point. The bulb of a thermometer of Type III is chilled to 5°C., wiped dry, and, while still cold, placed in the molten petrolatum so that approximately the lower half of the bulb is submerged. It is then withdrawn immediately and held in a vertical position away from the source of heat until the surface of the petrolatum becomes

dull in appearance, whereupon it is placed for 5 min. in a water bath having a temperature not greater than 16°C. The thermometer is then fixed securely in a test tube by means of a cork so that the lowest point is approximately 15 mm. above the bottom of the test tube. The test tube is suspended in water of 16°C. contained in a beaker, and the temperature of the bath is increased to 30°C., at a rate not exceeding 3° per min. When this temperature is reached, the rate of heating is reduced to 2° per min. The temperature at which the first drop of petrolatum is observed to leave the thermometer bulb is taken as the melting point. Freshly melted samples should be used for each determination. If three determinations show a variation that is not greater than 1°C., the average of the three values is taken. If the variation of three determinations is greater than 1°C., two additional determinations are made and the average of the five values is taken as the melting point.

Congealing Point.—Theoretically, the congealing point of a liquid should be identical with the melting point of the same substance in solid form. Actually, slight differences are frequently observed in these two values, especially when the determinations are made upon mixtures of substances rather than upon pure compounds. For the general purpose of identification and detection of impurities, the melting point is more commonly used. This is because ample data on melting points may be found in the literature for almost all well-known substances, while data on congealing points have been reported only for a limited number of substances.

A special procedure for the determination of congealing points is given under the section entitled Congealing Temperature on page 566 of the twelfth revision of the Pharmacopoeia. This method may be summarized as follows: About ten centimeters or grams of the melted solid is placed in a dry test tube having an internal diameter of 18 to 20 mm. The sample is then cooled in water, or a suitable freezing bath, to a point approximately five degrees below the supposed congealing point of the liquid. In order to induce congelation, the inner walls of the tube are rubbed with the bulb of the thermometer, or a small fragment of the substance being tested is added. By alternate immersion of the tube in the freezing bath or removal from it, constant stirring with the thermometer being maintained throughout, the temperature of the substance is so adjusted that the greater portion of the liquid gradually congeals. The highest temperature that remains constant for an appreciable period of time during the solidification of the liquid is taken as the **congealing point.**

Evaporation.—This term may be defined as the formation of a vapor from the surface of a liquid. Evaporation is usually

distinguished from boiling, or ebullition, a phenomenon that occurs only at one temperature (at a given pressure) for a given liquid. Evaporation may occur at any temperature, but only from the surface of a liquid. According to the molecular-motion theory of heat, it is assumed that the molecules of a liquid are constantly in motion but at the same time exert a mutual attraction upon each other. It is assumed that, as a result of their velocity, molecules of the liquid near the surface may pass into the space above the liquid. If the escaping molecules have sufficient velocity, they may go beyond the zone of attraction of the molecules in the liquid; but if the speed of the molecules is insufficient to overcome this attractive force, they will then be drawn back into the liquid.

Although a certain number of molecules may escape from the liquid at any temperature, the number of molecules lost by evaporation increases with an increase in temperature. When any substance, whether solid, liquid, or gas, is heated, the rate of vibration of the molecules, as well as the amplitude of vibration, is increased. Consequently, when a liquid is heated, the number of molecules near the surface possessing sufficient velocity to escape from the attraction of the molecules remaining in the liquid is correspondingly greater.

It has been observed that, when a liquid is allowed to evaporate spontaneously, *i.e.*, without the application of heat, the remaining liquid portion becomes cooler. This is especially noticeable in liquids that have a high vapor pressure, such as ether (537 mm. of mercury at 25°C., as compared with 23.7 mm. of mercury for water at the same temperature). This effect may be explained by the molecular-motion theory of heat. The reduction in temperature occurs because the molecules with the highest velocity of vibration, which means those possessing higher temperatures, are escaping from the liquid, leaving behind those with a smaller amplitude of vibration and correspondingly lower temperatures. Since additional heat (heat of vaporization) is needed to transform the liquid to a vapor, this is absorbed from the liquid, with the result that a considerable reduction in the temperature of the liquid is noted.

Heat of Vaporization.—In Chap. IX, under the **Steam Bath,** reference was made to the latent heat of vaporization of water in

explaining the greater efficiency of the steam bath over the water bath as a means of transmitting heat. Every liquid substance has a definite heat of vaporization which is peculiar to, and characteristic of, that particular liquid. This value may be defined as the number of calories of heat energy required to convert 1 Gm. of liquid at its boiling temperature into vapor of the same temperature. It will be recalled that the approximate value for the heat of vaporization of water is 537 cal. The heats of vaporization for a few of the common organic liquids are listed in Table XIX. Since the values for all the organic liquids listed are appreciably below the value for water, it follows that, at any given temperature below the boiling point, the rate of evaporation for all these substances will be greater than that for water.

TABLE XIX.—HEATS OF VAPORIZATION[1]

Compound	Heat of Vaporization, cal.
Acetone	124.5
Benzene	94.3
Carbon disulfide	84.1
Carbon tetrachloride	46.4
Chloroform	59.0
Ethyl acetate	88.4
Ethyl alcohol	204.0
Ethyl ether	83.9
Nitrobenzene	79.1

[1] Selected from a table appearing in the "Handbook of Chemistry," by N. A. Lange, Handbook Publishers, Inc., Sandusky, Ohio, 2d ed., 1937, p. 1149.

Vapor Pressure.—Evaporation will continue to take place from the surface of the liquid only so long as it is exposed to an unlimited and unsaturated atmosphere. If evaporation occurs within a closed space, that space eventually becomes fully saturated with vapor and at this point an exchange of molecules will occur at a constant rate between the liquid and the vapor phases. Thus a condition of dynamic equilibrium is reached, which means in effect that no further evaporation can occur. Under these conditions, the vapor contained in the closed space in contact with the liquid is known as a *saturated vapor*, and for a given temperature this pressure is constant for a given liquid. Liquids possessing high vapor pressures for a given temperature show a relatively higher rate of evaporation, or are said to be more volatile, than liquids with lower vapor pressures. It is inter-

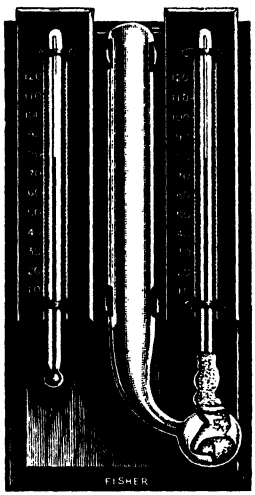
esting to note that, in accordance with **Dalton's law of partial pressures,** when more than one vapor is present in a closed system, the total pressure exerted by the mixture of vapors is equal to the sum of the pressures which each of the vapors would exert individually in the absence of any other vapor. This effect of total pressures of mixed vapors is of considerable significance with reference to fractional distillation and will be mentioned in that connection in Chap. XI.

Atmospheric Moisture.—The air does not usually contain all the water vapor it is capable of holding at a given temperature. Because the quantity of moisture required for saturation decreases with a decrease in temperature, it often happens, however, that a drop in temperature will cause dew to be formed or, at lower temperatures, frost to be produced. This is explained by the fact that the quantity of water vapor originally present is more than sufficient for saturation at the lower temperature. The temperature at which water vapor begins to condense is known as the **dew point.**

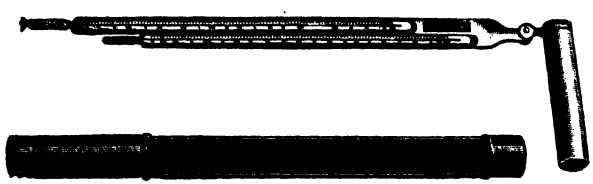
It is customary to refer to the quantity of water vapor in the air in terms of **humidity.** In meteorology, the expressions **absolute humidity** and **relative humidity** are commonly used. The former is used to indicate the quantity of water vapor actually present in the air at a given temperature and is usually expressed in weight units per unit of volume, as grams per cubic meter or grains per cubic foot. Relative humidity expresses, as percentage, the ratio between the quantity of moisture present and the quantity required at the same temperature for complete saturation. Thus, a relative humidity of 100 indicates complete saturation, while a value of 50 denotes that the quantity of moisture present is equivalent to one-half the amount required to attain saturation at the same temperature.

Determination of Relative Humidity.—Relative humidity is usually determined by the use of instruments called **hygrometers.** The principle employed is based on the difference in temperature readings shown by two thermometers, one with a dry bulb and one with a wet bulb. Advantage is taken of the fact that a liquid, as it evaporates, absorbs heat from its surroundings. Two thermometers are provided, the bulb of one being equipped with a wicklike device, which maintains it in a moist condition.

The rate of evaporation of the water is inversely proportional to the relative humidity in the surrounding atmosphere, being more rapid in relatively dry air and less rapid as the saturation point is approached. The more rapid the rate of evaporation, the greater the cooling effect upon the wet-bulb thermometer. The difference in the temperatures of the two thermometers is read



Mason hygrometer.



Sling psychrometer.

FIG. 69.—Hygrometers.

and converted into relative humidity by referring to special tables provided by the manufacturers of the instrument showing the relative humidity corresponding to the observed difference in temperature readings at any existing atmospheric temperature.

A modification of the wet- and dry-bulb type of hygrometer is illustrated by the sling psychrometer shown in Fig. 69. This differs from the instrument just described in that the two thermometers are mounted on a frame provided with a handle

and a swivel joint so that, after moistening the bulb of one of the thermometers, both may be whirled about rapidly in the air. Under these conditions of forced ventilation, more rapid evaporation occurs, correspondingly greater differences in temperature being shown by the two thermometers, as compared with the results obtained with the stationary wet- and dry-bulb thermometers. Accordingly, the values shown in the tables for conversion of readings obtained with this instrument take this effect into account and do not apply to the readings obtained with the stationary type of instrument.

Factors Influencing the Rate of Evaporation.—The rate of evaporation of a liquid at a temperature below its boiling point is influenced by a number of factors. These factors are (1) the surface area exposed, (2) the concentration of the vapor in contact with the liquid, (3) the pressure on the surface of the liquid, (4) the temperature of the vapor, and (5) the temperature of the liquid.

1. The Surface Area Exposed.—It has been shown by Dalton that, at a given temperature, the rate of evaporation, expressed in terms of the mass of vapor produced per unit of time, is proportional to the area of the surface exposed. For example, if at a given temperature a liquid is evaporated in a square pan, having the dimensions of 6 in. on each side, the number 36 (6×6) may be used to express the rate of evaporation. On the other hand, if the same quantity of liquid is placed in a square container 3 by 3 in. in size, the value 9 (3×3) would represent the relative rate of evaporation. These relationships would exist only if all other factors remain constant. Practical application of this principle has been made in designing the shape of evaporating dishes, which are usually of wide diameter and relatively shallow depth in order to expose the greatest possible surface as an aid in speeding up the process of evaporation. The effect of increased surface may also be gained in another way, namely, by agitating or stirring the liquid while it is being evaporated. As the liquid is moved about, a relatively greater surface of the liquid is exposed to the surrounding atmosphere than would be the case if the liquid were left undisturbed. In industrial processes where evaporation is used as a means of absorbing heat (refrigeration), the use of sprinkler systems by means of which the liquid to be evaporated is forced into fine streams or spray represents a practical application of this principle. The surface of the liquid exposed to contact with the atmosphere is increased in this manner as a means of increasing the rate of evaporation.

2. Concentration of the Vapor.—If all other factors remain constant, the rate of evaporation is proportional to the concentration of the vapor in the atmosphere immediately above the liquid. As has already been indi-

cated, when evaporation takes place within a closed container, the atmosphere above the liquid soon becomes fully saturated, with the result that no further evaporation can occur. A more accurate statement of the influence of this factor upon the rate of evaporation would be to say that the rate of evaporation is proportional to the difference between the maximum vapor pressure of the liquid in question and the pressure due to the vapor actually present in the atmosphere immediately above the liquid. Thus it is evident that, when these two pressures become equal, there can be no evaporation and that the maximum rate of evaporation will be attained when the con-

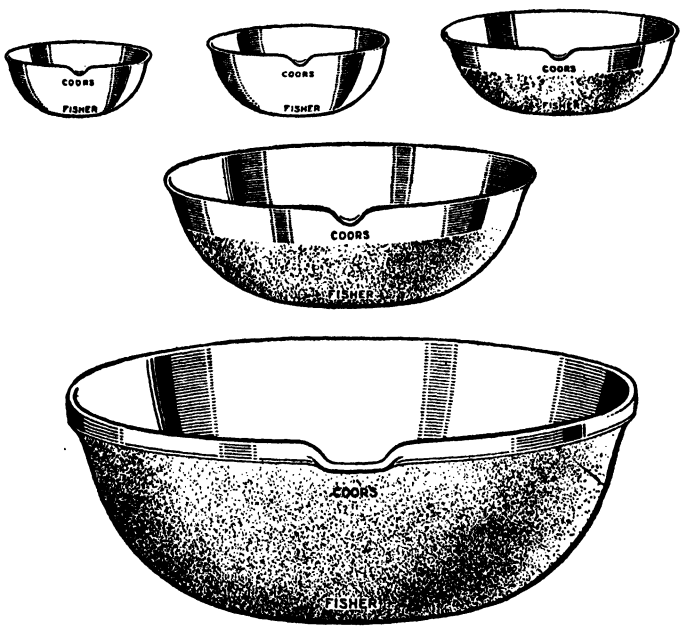


FIG. 70.—Evaporating dishes.

centration of the vapor in the atmosphere surrounding the liquid is equal to zero. This explains the advantage of providing for the free circulation of air during evaporation. A current of air from a fan or other source will materially increase the rate of evaporation of a liquid.

3. THE PRESSURE ON THE SURFACE OF THE LIQUID.—If all other factors remain constant, the rate of evaporation is inversely proportional to the pressure on the surface of the liquid. This means in effect that, if the pressure is reduced by one-half, the rate of evaporation will be doubled. This may be explained from the standpoint of the resistance of the pressure to the movement of molecules. When the pressure is reduced, less resistance to the movement of the molecules is offered, they are able to attain a higher velocity, and a relatively greater number are able to escape from the liquid

in a given period of time. Practical application of this principle is made in the use of vacuum desiccators, vacuum drying ovens, vacuum pans, etc., which are used for the removal of moisture or other liquids from solid or liquid substances.

4. THE TEMPERATURE OF THE VAPOR.—A vapor that is saturated at one temperature will be unsaturated at a higher temperature. Conversely, if a saturated vapor is cooled, some of the vapor condenses and becomes liquid. It has already been pointed out that no evaporation can occur in the presence of a saturated vapor and that the rate of evaporation increases as the concentration of the vapor is decreased. It must follow that the rate of evaporation may be increased by increasing the temperature of the vapor. Some idea of the effect of this factor may be obtained from the fact that 1 cu. M. of air will contain, if fully saturated, about 12 Gm. of water vapor at 15°C., 82 Gm. at 50°C., and as much as 234 Gm. at 75°C. This explains why evaporation takes place more rapidly in warm air than in cold air.

5. THE TEMPERATURE OF THE LIQUID.—The molecular-motion theory of heat also serves to explain why the rate of evaporation is increased by a rise in temperature. As has been previously mentioned in the general discussion of evaporation, the effect of heat is to increase the rate of vibration of the molecules of a liquid, as well as the amplitude of their vibrations. It follows that, as the temperature is increased, a correspondingly greater proportion of the molecules will attain sufficient velocity to overcome the force of cohesion of the molecules of the liquid phase and to escape as a vapor. It may be stated that the rate of evaporation will be directly proportional to the temperature of the liquid, if all other factors remain constant. This relationship holds true only for temperatures below the boiling point of the liquid in question.

Ebullition.—As has been pointed out in the discussion of steam baths, in Chap. IX, when heat is applied to a liquid, a more or less uniform increase in temperature occurs until the vapor pressure of the liquid just exceeds the atmospheric pressure. At this point, the temperature remains constant, even with additional heating, and bubbles of vapor are observed to arise throughout the liquid. This means that evaporation is occurring, not only from the surface of the liquid, but within the liquid itself. This phenomenon is known as **ebullition** or **boiling.** For pure liquids, the temperature of boiling is a physical constant that is characteristic of the particular liquid being tested and serves, not only as a useful means of identification, but for the detection of impurities. Since the boiling point of a liquid is a constant value only at constant pressure, barometric readings must be taken in order to determine true boiling points.

The Barometer.—The usual method of measuring atmospheric pressure is by means of the barometer. This instrument owes its origin to the experiments of Torricelli, who, in 1643, devised a method for measuring the resistance that is offered by nature to a vacuum by making use of a column of mercury. If a glass tube about 3 ft. in length is closed at one end and completely

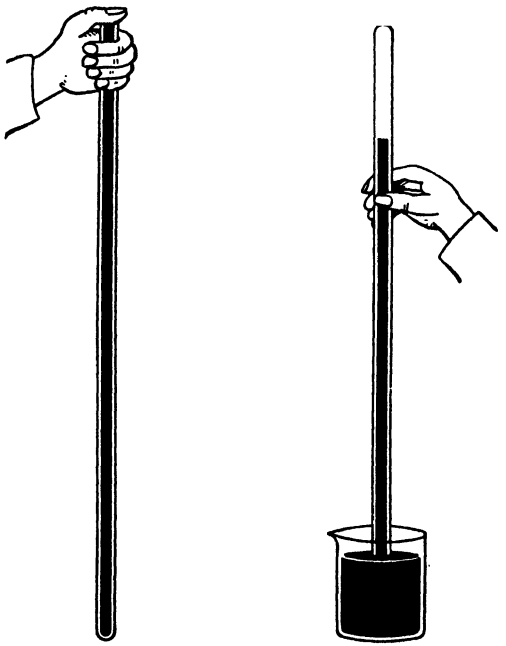


FIG. 71.—Torricellian tube.

filled with mercury, and then, while the opening is closed with the finger in order to prevent the escape of mercury from the tube, if the tube is inverted and the open end immersed in an open dish of mercury, it will be noted that the mercury sinks to a level of approximately 30 in. (29.92 in.). The weight of the column of mercury in the tube is in equilibrium with the pressure of the atmosphere on the mercury contained in the dish below. According to Pascal's law concerning the uniform distribution of pressure in a liquid, the pressure of the column of mercury at its lower end must be equal to that on the surface of the mercury outside the tube. The column of mercury is of known

height, 29.92 in. (or approximately 760 mm.). If we assume that the area of the column is equivalent to 1 sq. cm., the volume of mercury in the column would be 76 cc., which, when multiplied by 13.6, the specific gravity of mercury, gives a weight of approximately 1,034 Gm. This is the atmospheric pressure that is exerted on 1 sq. cm. of area. When converted into the English system, this value is equivalent to approximately 14.7 lb. per sq. in.

Boiling-point Determinations.—The twelfth revision of the Pharmacopoeia describes the physical constant of liquids, commonly known as the boiling point, under the title Boiling or Distilling Temperatures, page 559. In reality, many liquids show not a true boiling point, but a range of boiling-point temperatures from the minimum to the maximum temperature registered during the process of distillation. The minimum boiling point is defined by the Pharmacopoeia as "The temperature shown by the thermometer when the first 5 drops of the liquid have been collected from the condenser." The maximum boiling point is said to be "The temperature at which the last liquid evaporates from the bottom of the flask or when the proportion specified in the text has been collected." The text to which reference is made in this statement is the official monograph for the liquid in question.

Two procedures are given in the Pharmacopoeia for the determination of boiling points. Method I is intended for use with liquids for which the permissible range in boiling temperature is 5°C. or less. Method II is to be used for liquids for which the permissible range in boiling temperature exceeds 5°C. For detailed information on these two methods, the official procedures should be consulted. The essential difference in the two methods is in the prescribed rate of distillation and the relative proportion of liquid to be distilled in each case.

The Effect of Barometric Pressure on Boiling Points.—As has already been indicated, the boiling point of a given liquid remains constant only at constant pressure. For the purpose of comparison, a pressure corresponding to 760 mm. is taken as a standard value, and observed boiling points are corrected with reference to this pressure. Although atmospheric pressure varies from time to time in a given location, the mean value at sea level

corresponds to this value. Aside from minor fluctuations that occur with changing weather conditions in a given locality, relatively greater variation is produced with a change in altitude. It has been estimated that a decrease in barometric pressure with increase in altitude occurs at the rate of 1 mm. of pressure for each 11 M. of increase in altitude. This corresponds to approximately 0.1 in. for each 90 ft. of increase in altitude.[1] Applying this ratio to the altitude corresponding with the summit of Pikes Peak, which is 14,109 ft. above sea level, we should have the following calculation:

$$\frac{14{,}109}{90} = 156.76 \times 0.1 = 15.67 \text{ in. of mercury}$$

Since the normal atmospheric pressure at sea level corresponds to 29.92 in. of mercury, $29.92 - 15.67 = 14.25$ in. of mercury, which would correspond to the mean atmospheric pressure at this elevation. When converted to the metric system, this is equivalent to 361.95 mm. of mercury, which is seen to be less than half the normal atmospheric pressure at sea level.

The procedures for Method I and Method II of the Pharmacopoeia require that corrections in the observed temperature readings shall be made for any variation in the barometric pressure from the normal (760 mm.) by allowing 0.1° for each 2.7 mm. of variation, adding if the pressure is lower, or subtracting if higher than 760 mm. Although the source of this factor is not given by the Pharmacopoeia, it appears to be derived from the data on the variation in boiling points of water at different pressures. A table of such values[2] entitled Boiling Points of Water at Various Pressures shows that water boils at 100.00°C. at 760 mm. pressure and at 99.63°C. at 750 mm. pressure. Thus a reduction of 10 mm. in pressure corresponds to a depression in the boiling point of 0.37°C. In order to find the decrease in pressure necessary to produce a reduction in the boiling point of 1°, we should perform the following calculation:

$$\frac{1.0}{0.37} \times 10 = 27.0 \text{ mm.}$$

[1] N. H. Black. "An Introductory Course in College Physics," The Macmillan Company, New York, 1935, p. 85.

[2] N. A. Lange. "Handbook of Chemistry," Handbook Publishers, Inc., Sandusky, Ohio, 2d ed., 1937, p. 1209.

Hence, a decrease of 27 mm. in pressure corresponds to a depression in boiling point of 1°C., or 2.7 mm. decrease in pressure corresponds to 0.1°C. depression in boiling point, which is the relationship used in the correction of boiling points in the official method. It should be noted that the Pharmacopoeia recommends this correction factor for all classes of liquids, despite the fact that its value is based upon the behavior of water. It follows that a certain amount of error is introduced in applying the correction for water to other liquids, since all liquids do not respond in the same way to changes in barometric pressure. This procedure probably is followed because of lack of specific information on the influence of barometric pressure on the boiling points of other liquids. It should therefore be understood that the correction, when applied to liquids other than water, represents only an approximation of the correction due to variation in pressure, rather than its true value.

With an extreme variation in barometric pressure, such as that computed for the pressure at Pikes Peak, as compared with the pressure at sea level, the decrease in the boiling point of water is considerable. As indicated in the calculation previously given, the barometric pressure at an altitude of 14,109 ft. would normally correspond to 14.25 in., or 361.95 mm., of mercury. In order to compute the boiling point of water at this pressure, one should proceed as follows:

$$760 - 361.95 = 398.05$$
$$\frac{398.05}{2.7} \times 0.1 = 14.74°C.$$
$$100.00 - 14.74 = 85.26°C.$$

Thus, theoretically, water should boil at 85.26°C. at this altitude. It should be noted, however, that, in these calculations, no correction has been made for the decrease in atmospheric temperature with increase in altitude. Since a decrease in its temperature results in an increase in the density of the atmosphere, this would tend to increase slightly the barometric pressure, which, in turn, increases the boiling point to a temperature somewhat higher than the value shown. Nevertheless, the decrease in the boiling point of water that occurs explains the difficulty of cooking vegetables by boiling at high altitudes. Because of the lower

temperature at which the water boils, the process must be continued for a relatively longer period of time. In such locations, the use of the pressure cooker is especially advantageous.

Desiccation.—The verb **to desiccate** is derived from the Latin *de* + *siccare*, to dry, from *siccus*, dry. (According to Webster's New International Dictionary, 2d ed., the verb means to dry up; to deprive or exhaust of moisture; to preserve by drying, as fish, fruit, or eggs.) In its application to pharmacy, the term **desiccation** is usually understood to mean the removal of water (in the form of sensible moisture) from animal and vegetable drugs, either at room temperature or by the use of moderate amounts of heat. In the broad sense, the term has many applications in domestic economy. For example, the drying of the freshly laundered clothing when hung out on the clothesline and exposed to the air is a typical example of desiccation.

As used in pharmacy, the process of desiccation is a most important step in the preservation of fresh drugs. In their original state, the fresh material may contain as much as 70 to 80 per cent, by weight, of moisture. If the material in its natural state is closely packed into containers as it is collected, the high percentage of moisture present permits a number of changes to occur. Certain types of fermentation may begin, accompanied by the development of considerable heat. This may result in considerable damage to the product as the result of chemical changes that are induced at the higher temperature. Furthermore, the presence of the moisture makes possible the growth of molds, which renders the product unfit for medicinal use. If, instead of packing the material in containers immediately upon collection, it is scattered out or hung up to dry in an attic or loft, gradual evaporation of the moisture occurs and there will be no evidence of the growth of molds. The drying of tobacco and the curing of freshly cut hay are common examples of this process.

After the material has lost the major portion of its moisture, it will be found that it has become friable, or brittle. This greatly facilitates the milling, or mechanical subdivision, of the drug. Further advantages arise from the reduction in bulk of the material. Since as much as four-fifths the weight is eliminated and since the water that is removed has no medicinal value, the

dried material is much more concentrated. This is a distinct advantage in that the individual dose is reduced to a size more convenient for administration. The decrease in weight also brings about a saving in transportation cost, which is of considerable importance from a commercial point of view.

For most drugs it has been found that a slow process of drying, such as that which results when desiccation is carried out at atmospheric temperature, gives the most satisfactory results. If it is desirable to hasten the process, this may be done by supplying heat artificially. Suitable precautions must be taken to use only moderate heat, for higher temperatures may have a deleterious effect upon the chemical constituents that are responsible for the desired therapeutic action of the drugs. This is especially true because, in the presence of moisture, certain natural substances, such as enzymes and oxidases, that are widely distributed in the plant kingdom are likely to induce more extensive reactions under the stimulus of moderate heat. If heat is to be employed, it is frequently applied by means of a drying closet, which is usually provided with forced circulation of air and equipped with a thermostat for the purpose of limiting the temperature. As explained in the discussion of Evaporation (page 287), an increase in the temperature of the atmosphere results in a corresponding increase in the rate of evaporation.

It is sometimes necessary to remove the last traces of moisture from certain types of nonaqueous liquid, such as volatile oils or mixtures of hydrocarbons. This may conveniently be accomplished by the use of certain anhydrous salts, which have a strong tendency to absorb water. Care must be taken to select a drying agent that is insoluble in the liquid to be dehydrated and that does not affect any of the constituents of the liquid chemically. Exsiccated sodium sulfate is widely used, especially in the treatment of volatile oils. Fused calcium chloride is also useful for this purpose. However, it must be remembered that this salt has the property of forming addition products with constituents of certain volatile oils, and its use should be avoided in such cases. On the other hand, it is widely used in the dehydration of mixtures of hydrocarbons.

In the isolation of substances from their solutions and their subsequent purification, the removal of the last traces of the

mother liquor is often desired. In some instances, because of the low melting point of the substance or its lack of stability at higher temperatures, the use of heat for this purpose is precluded. In such cases, the liquid may be removed by placing the substance upon bibulous paper, such as filter paper or blotting paper, or upon a porous (unglazed) porcelain plate. Because of the porosity of these materials, the excess liquid is quickly absorbed by capillary action.

Desiccators.—Another way of increasing the rate at which desiccation occurs, but at the same time maintaining room temperature, involves the use of chemical dehydrating agents in special containers called **desiccators.** These are usually circular in shape, made of heavy-walled glass, and provided with a lid having a ground surface, which, when lubricated with petrolatum or a mixture of beeswax and petrolatum, produces an airtight closure. The usual style of desiccator is separated into an upper and a lower compartment by a constriction near its center, and a perforated porcelain plate rests on the shelf formed by the recessed portion as a support for the containers (crucibles, or dishes) for the material to be dried. The lower compartment is used for the **dehydrating agent.** In order to avoid absorption of moisture from the atmosphere, the desiccator should be kept closed at all times except when it is necessary to open it in transferring crucibles containing material to be dried. A special type of desiccator made of spun aluminum has been recently developed. This has the advantage of lighter weight and is not subject to breakage. However, a special drying agent, exsiccated aluminum oxide (known as Activated Alumina), must be used with the aluminum desiccator, since other chemicals used as drying agents cause the metal to corrode.

Among the drying agents that may be used in glass desiccators are the following: anhydrous calcium chloride, concentrated sulfuric acid, solid potassium hydroxide, solid sodium hydroxide, soda lime, unslaked lime, phosphorus pentoxide, and magnesium perchlorate.[1] Some of these are more widely used than others, partly because of their lower cost. They also vary considerably

[1] Manufactured under the copyrighted name of Dehydrite, a trihydrated form of magnesium perchlorate, by the G. Frederick Smith Chemical Co., Columbus, Ohio.

in their efficiency. One of the most efficient agents, although seldom used because of its cost, is phosphorus pentoxide. Concentrated sulfuric acid is almost equally efficient, but is less

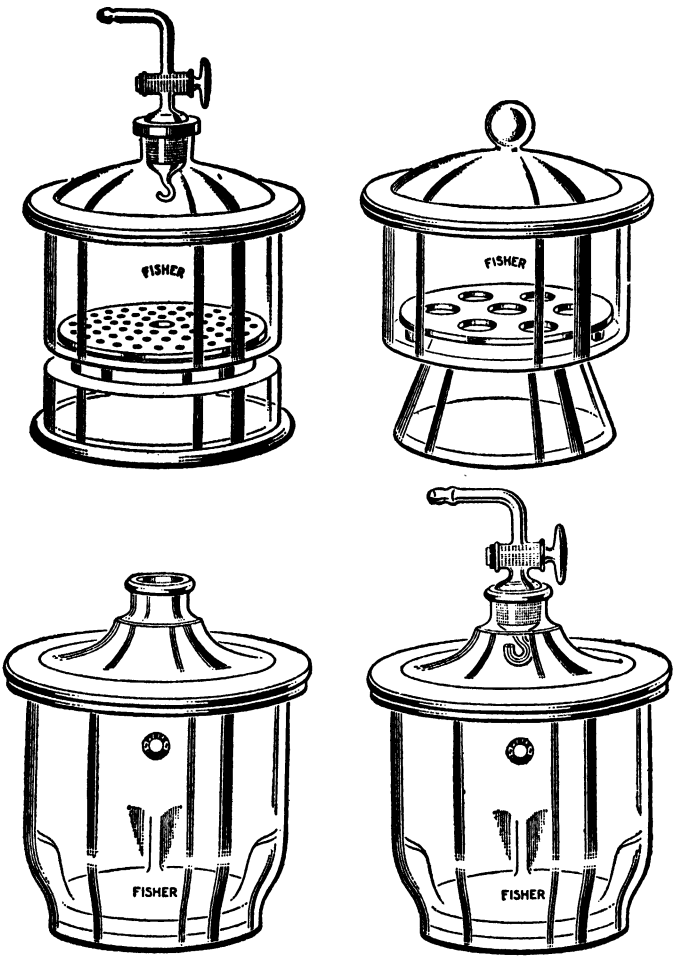


FIG. 72.—Desiccators.

desirable because of its physical form. Since sulfuric acid is a liquid, great care must be exercised in moving the desiccator from place to place to avoid splashing the acid onto the containers or even into the material being dried. Probably the

most widely used agent of all is anhydrous calcium chloride. It is much safer to use because it is solid in form, and although it is relatively a less efficient agent than sulfuric acid the advantage of low cost and greater safety have led to its widespread use. The drying powers that these substances possess are for the most part due to the attraction, or affinity, that they have for moisture. In the case of sulfuric acid, the absorption is due to the characteristic property of this substance of attracting water in order to form hydrates containing a higher proportion of water molecules. In the case of sodium and potassium hydroxides, advantage is taken of the natural tendency of these substances to absorb water up to the point of deliquescence (when liquefaction due to solution of the substance in the absorbed water occurs). The anhydrous calcium chloride and the magnesium perchlorate represent completely or partly exsiccated salts, which are quite unstable in a moist atmosphere and have a strong tendency to absorb more water in order to form hydrates containing a higher proportion of water molecules. The absorption of water by unslaked lime and phosphorus pentoxide involves a chemical reaction in which the water combines with the oxides to form hydroxides.

A widely used desiccator of another type is the vacuum desiccator, which differs from the plain desiccator in that provision is made for partly exhausting the air within the chamber. In practice, extremely low pressures are avoided because of the danger of collapsing the desiccator. The theoretical explanation of the advantage of reduced pressure as an aid in the drying process is based on the principle previously mentioned in the discussion of Evaporation (page 293), in which it was pointed out that the rate of evaporation is inversely proportional to the pressure on the liquid. If desired, the use of partial vacuum or reduced pressure may be combined with the drying action of dehydrating chemicals in the same desiccator, provided that the necessary care is exercised in relieving the vacuum before opening the desiccator in order to avoid disturbing the drying agent by the gusts produced by a sudden influx of air, which might result in accidental contamination of the material being dried.

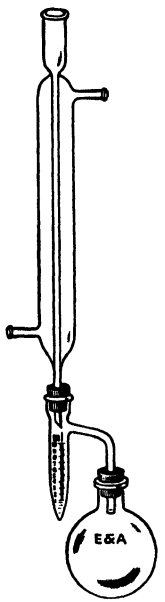
Determination of Moisture in Vegetable and Animal Drugs.—Official methods for the determination of moisture in animal and

vegetable drugs are described in a series of monographs in the twelfth revision of the Pharmacopoeia, pages 629 to 630. For drugs containing no constituents volatile at 100°C., a representative sample, suitably prepared and weighing about 10 Gm., is dried at a temperature of 100°C. for 5 hr. and weighed. The drying is continued, with weighings at 1-hr. intervals, until the loss in weight during a given hour's heating does not exceed 0.25 per cent of the original weight.

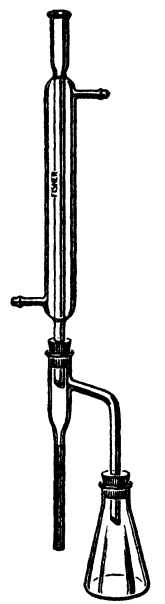
A special procedure is described for drugs containing ether-soluble constituents volatile at 100°C. The loss in weight that occurs when the drug is subjected to the drying process outlined for drugs containing no constituents volatile at 100°C. is first obtained. A determination of the volatile ether-soluble extractive is then made on another sample by the following procedure: The sample is dried over sulfuric acid for not less than 12 hr. and then subjected to extraction with absolute ether in a continuous extraction apparatus for a period of 20 hr. The resulting ethereal solution is then permitted to evaporate spontaneously, dried over sulfuric acid for 18 hr., and weighed. The extract is gradually heated to 110°C., and the heating is continued until the weight is constant. The loss in weight of the extract represents its volatile portion. The percentage of volatile ether-soluble extractive is then subtracted from the percentage loss in weight upon drying at 100°C., in order to obtain the percentage of moisture in the sample.

A third method of general application in the determination of moisture in vegetable and animal drugs is described in the Pharmacopoeia under the heading Moisture Method by Toluene Distillation. The procedure requires the use of a moisture-determination tube especially designed for the purpose and consists in a volumetric determination of the water distilled from the drug in the presence of toluene vapor. This particular hydrocarbon is well adapted to this use because it is practically immiscible with water; it has a boiling point above that of water (110.8°C.); and its specific gravity (0.866) is less than that of water. When toluene is placed on the drug and distilled, the moisture contained in the drug is also vaporized and entrapped as it condenses in the graduated portion of the tube beneath a layer of toluene. The size of the sample of drug is so adjusted

that the volume of water obtained will fall within the limits of the capacity of the tube. The contents of the tube are permitted to cool to room temperature before final readings are made. The maximum capacity of the tubes may vary from 5 to 10 cc., with subdivisions of 0.1 cc.



Stark and Dean distilling trap.



Bidwell and Sterling distilling trap.

FIG. 73.—Moisture determination tubes.

Exsiccation.—This noun is derived from the verb **to exsiccate,** which in turn is derived from *ex*, out, and *siccare*, to dry. (According to Webster's New International Dictionary, 2d ed., the verb means to exhaust or evaporate moisture from; to dry up.) A comparison of the derivation of this term with that given for **desiccation** shows little, if any, difference in meaning; according to the dictionary, the two terms could be considered synonymous. In their pharmaceutical applications, however, the terms have separate and distinct meanings that are well understood by pharmacists, despite the similarity in their etymology. Although exsiccation may accomplish the same object as that described under Desiccation, the process is more extensive and implies the complete removal of all water, including water of hydration,

or crystallization, from crystalline salts, ordinarily by the use of higher temperatures than those employed for desiccation. Thus, the essential difference between the two terms is that desiccation is limited to the removal of water in the form of sensible moisture, while exsiccation includes the removal of water of hydration from crystalline salts.

Water of Hydration.—Many chemical compounds, upon separation from their saturated aqueous solutions in crystalline form, combine with water in a definite proportion. In the earlier textbooks on chemistry, the water that combined in this way was known as water of crystallization. However, many other compounds, both inorganic and organic, do not combine with water to form crystalline structures, indicating that the water is not always essential to crystal formation. Accordingly, the older term *water of crystallization* is gradually being replaced by *water of hydration.*

A common example of a salt that crystallizes from water with water of hydration is copper sulfate. In its crystalline condition, this compound is blue in color, and it produces a blue solution when dissolved in water. If the crystalline salt is heated, it gradually gives up its water of hydration and is converted into a white substance. If the loss in weight is determined, it will be found that five molecules of water are liberated from each molecule of the crystalline substance. Hence, the formula for the blue crystalline salt is written as $CuSO_4 \cdot 5H_2O$. It is written in this way rather than as $CuSO_9H_{10}$ to indicate that, while it represents a chemical compound formed in accordance with the rules of definite proportions, the water of hydration is not firmly united as are other components of chemical compounds and may readily be removed upon the application of heat. It is possible to think of such combinations as rather unstable complex compounds, or molecular associations in definite proportion, rather than as stable chemical entities. The ordinary theories for valence will not account for the reaction between the anhydrous substance and the water of hydration, and the exact method of formation of such hydrates is not fully understood.

Although we speak of the combined water as water of hydration, it should be understood that it does not exhibit the usual properties of water when combined as a hydrate. For example,

crystalline copper sulfate may be reduced to an impalpable powder without showing the slightest trace of moisture. It is only when heat is applied and the water of hydration is liberated from the anhydrous compound that it may be detected either as water or water vapor.

As already indicated, many substances readily form hydrates when crystallized from aqueous solutions, while others do not. There seems to be little uniformity in this tendency. Combinations of this type are more common among the inorganic salts than among the organic substances. Wide differences are also noted in the stability of those hydrates which are formed. It is believed that the hydrates possess definite aqueous tensions at definite temperatures and that the hydrate decomposes and the anhydrous substance fails to combine with water when the pressure of the water vapor in the surrounding atmosphere is greater than the aqueous tension of the hydrate. A hydrate that tends to lose its water of hydration at ordinary conditions of temperature and moisture content of the air is said to be **efflorescent.** On the other hand, many crystalline salts have so great an attraction for moisture that they may absorb a sufficient quantity from the atmosphere (especially when the humidity is high) to become liquefied by dissolving in the absorbed moisture. Such salts are said to be **deliquescent.** Some common examples of deliquescent compounds are the following: aluminum chloride; calcium bromide; calcium chloride; lithium bromide; lithium citrate; potassium acetate; potassium hydroxide; sodium hydroxide; trichloracetic acid; zinc chloride. The following are examples of efflorescent salts; copper sulfate; ferrous sulfate; lead acetate; magnesium sulfate; sodium acetate; sodium borate; sodium carbonate; sodium phosphate; sodium sulfate; zinc acetate; zinc sulfate.

In its application to pharmacy, the process of exsiccation is of value in only a limited number of cases. Since the process results in a decrease in the bulk of the product, it is sometimes used advantageously for those compounds which are to be administered in individual dosage forms, such as pills, capsules, and compressed tablets, in order to keep the bulk of the pill, capsule, or tablet at the minimum for greater ease of administration. More frequently, the process is carried out upon those

compounds which are to enter into granulation mixtures, intended for compressed tablets or granular effervescent salts, for the purpose of avoiding the difficulties due to chemical or physical reactions which would otherwise follow as the water of hydration is liberated when the granulation mixture is subsequently heated. Only three exsiccated compounds are recognized in the twelfth revision of the Pharmacopoeia, namely, Exsiccated Alum, Exsiccated Sodium Phosphate, and Exsiccated Sodium Sulfite, while the National Formulary VII lists Exsiccated Sodium Arsenate only.

Torrefaction.—According to Webster's New International Dictionary, 2d ed., this word is derived from the very **torrefy,** French *torréfier*, from the Latin *torrefacere*, from *torrere*, to parch, and *facere*, to make. It means to subject to heat, to dry or roast by fire, to parch, to scorch. A special definition for the term as used in pharmacy is also given as follows: to dry or parch, as drugs, on a metallic plate till they are friable or are reduced to the state desired. Although the pharmaceutical application of this process has become obsolete, it is still widely used in the processing of numerous food products. It involves the moderate heating of organic material for the purpose of modifying or developing the taste, aroma, odor, and color of these products. The changes that occur are mild in nature, being limited in their extent by the relatively low temperatures employed. A familiar application of this process is found in the roasting of coffee. As harvested, the coffee bean has an entirely different color and odor from those of the roasted product. The rich brown color and the characteristic odor and flavor result from the effect of heat on certain constituents that are naturally present. In a similar manner, the development of the characteristic chocolate flavor is dependent on the roasting of the theobroma seeds from which this product is derived. The roasting of peanuts is another familiar example of torrefaction.

Although no longer in use, a product known as torrefied rhubarb was formerly widely employed in pharmacy. Rhubarb is one of a number of drugs containing a principle known as **emodin,** which is valued because of its cathartic action. At the same time, it contains considerable amounts of **tannins,** which are astringent in character and which act as an antidysenteric, an action almost directly antagonistic to the cathartic action of emodin. It has long been known that if rhubarb is subjected to mild heating, or torrefaction, the emodin is destroyed and rendered physiologically inert, while the tannins are apparently unchanged. Accordingly, torrefied rhubarb was used as an antidysenteric until replaced by other tannin-bearing drugs that are devoid of emodin and require no special treatment prior to use.

Carbonization.—This term is used to describe a process in which organic matter is heated to a relatively high temperature

without access to air. The procedure followed in the manufacture of charcoal serves as an example of this process. Although the modern method requires the use of kilns, originally the process was carried out in deep pits dug in the ground. Wood was placed in the pits and ignited; then earth was shoveled over the burning wood in sufficient quantity to smother the flame, and the wood was allowed to smolder until the fire was extinguished. Under these conditions, incomplete combustion occurred, because of the lack of oxygen, the hydrogen and oxygen originally contained in the wood combining to form water vapor or intermediate products of decomposition, while most of the carbon remained as a residue. If the same operation were carried out with free access to air, complete combustion, or **incineration,** would occur and the wood would be reduced to ash. Almost any organic substance, when heated in a closed space to a sufficiently high temperature, will undergo carbonization.

There is a close relationship between **carbonization** and **destructive distillation,** which is discussed in Chap. XI. If the vapors given off during carbonization are collected and condensed, a mixture of substances is obtained which represents products of less complex nature than the natural constituents from which they are formed. In the destructive distillation of wood, such products as acetone, methyl alcohol, acetic acid, creosote, and tar are secured. By the same process, coal yields illuminating gas, ammonia, and coal tar, from which phenol, cresol, benzene, toluene, xylene, and many other substances may be obtained.

The product occurring as a result of carbonization is an extremely useful substance, not only in pharmacy, but in many branches of industry. Because of its porosity, it possesses remarkable adsorptive powers, serves as a decolorizing agent and a deodorant, and is widely used in the purification of organic substances in organic synthesis or in the isolation of such products from natural sources. Although wood charcoal is no longer official in the Pharmacopoeia, the variety most widely used in the past was that derived from willow wood. Charcoal may be prepared from many other sources. Animal charcoal is recognized in the National Formulary VII, under the title Purified Animal Charcoal, and is defined as charcoal prepared from bone

and purified by removing the substances that are dissolved by hot hydrochloric acid and water.

A product that has come into wide use within recent years is recognized in the Pharmacopoeia as Activated Charcoal (Carbo Activatus) and is available under a number of copyrighted names, such as Darco and Norite. The pharmacopoeial definition of this substance reads as follows: "The residue from the destructive distillation of various organic materials, treated to increase its adsorptive power." In practice, much of the commercial activated charcoal is obtained by the incomplete combustion of crude petroleum oil by means of special burners designed for this purpose. After the carbon has been deposited in the form of fine soot, it is subjected to special treatment in order to increase its adsorptive powers. Although the technical processes may vary with different sources of carbon, one variety of treatment involves the exposure of the material to superheated steam at relatively high temperatures or heating in the presence of some inert gas. As a result of such treatment, the adsorptive powers are increased to eight or 10 times that of ordinary wood charcoal. The relative adsorptive powers may be tested by determining the minimum amounts of the two varieties of charcoal required to decolorize completely test solutions containing a dye. A special test involving the use of methylthionine chloride (methylene blue) is outlined in the Pharmacopoeia.

Activated charcoal is extremely useful in removing undesirable color from solutions and liquid preparations; but it must be remembered that not only is the offending color removed, but other dissolved substances in the solution are likely to be adsorbed from the solution at the same time. Although the remarkable powers of adsorption that are developed by the activation of charcoal are not fully understood, it is believed that the process of adsorption involves condensation of the adsorbed substance on the surface of the charcoal and that the increased capacity for such surface condensation is the result of an increase in the exposed surface of the activated charcoal. Since wood charcoal (Carbo Ligni) is no longer official, the Pharmacopoeia states that, when this is prescribed, activated charcoal may be dispensed.

Calcination.—This term is derived from the verb **to calcine** from the French *calciner*, Latin, *calx*, and means to reduce to a

powder, or to a friable state, by the action of heat; to heat so as to expel volatile matter, as carbon dioxide from limestone, and thus disintegrate; as, to *calcine* bones. In its pharmaceutical application, the term **calcination** means the separation of volatile from nonvolatile matter by the application of heat without fusion. The process is usually applied to inorganic matter and requires relatively high temperatures. Its principal use in pharmacy is in the expulsion of carbon dioxide from carbonates, leaving the oxide as a residue.

As already indicated the word is from the Latin *calx*, lime (calcium oxide). Calcination is, therefore, literally the manufacture of lime. Although it may be applied to other substances, it is usually employed only in the treatment of limestone to produce lime or magnesium carbonate to form magnesium oxide.

Ignition and Incineration.—The term **ignition** is derived from the verb **to ignite** from the Latin *ignitus*, past participle of *ignire*, to ignite, from *ignis*, fire. According to Webster's New International Dictionary, 2d ed., this verb means to subject to the action of fire or intense heat; to heat strongly; to render luminous by heat; as, to *ignite* iron or platinum; also, to kindle, to set on fire; as, to *ignite* paper or wood.

This definition is not entirely precise, but the term *ignition* is used by pharmacists to indicate the strong heating of inorganic material or matter that consists principally of inorganic substances and refers to a process of considerable importance in gravimetric analysis. Pharmacists attempt to distinguish between **ignition,** which involves the action of heat upon incombustible substances, and **incineration,** which represents the action of strong heat on combustible matter, usually of organic origin. If, for example, in the determination of the sulfate radical in a gravimetric analysis, an excess of barium chloride test solution is added to the solution of the sulfate, a precipitate of barium sulfate will be formed. The barium sulfate that is produced is then collected on a filter, washed to remove soluble impurities, dried, and ignited. The object of igniting the barium sulfate, which is incombustible, is to remove the last traces of volatile impurities that might be present.

If, on the other hand, a sample of a vegetable drug, such as belladonna leaf, is carefully weighed and subjected to strong heat

with free access to air, almost complete combustion will occur and, if the sample conforms to the pharmacopoeial requirement, the weight of the residue, known as *ash*, will not exceed 3 per cent of the original weight of the sample. This residue consists entirely of nonvolatile inorganic compounds, such as the carbonates and oxides of calcium, magnesium, iron, sodium, and potassium, which were originally present in the leaf. All organic matter has been completely destroyed and driven off. The procedure just described is an example of incineration rather than ignition. The word is derived from the medieval Latin *incineratus*, the past participle of *incinerare*, to incinerate, from *in* + *cinis, cineris*, ashes, and means to burn to ashes, to consume or be consumed by fire.

Deflagration.—This term is derived from the Latin *deflagratus*, past participle of *deflagrare*, from *de* + *flagare*, to flame, burn. When the term is used with reference to its chemical and pharmaceutical applications, it usually means the process of strong heating, accompanied by minute explosions such as would occur when mixtures of charcoal and potassium nitrate are heated to high temperatures. The decomposition that takes place is often accompanied by repeated crackling sounds, and the substance being heated has a tendency to fly from the crucible, because of the explosive violence of the reaction. As a rule, those inorganic substances which are rich in oxygen, such as the nitrates and chlorates, exhibit this behavior. As the salt reaches the temperature at which it decomposes, minute pockets of oxygen are produced within the mass of the individual crystals, which exert sufficient pressure to cause them to be split asunder. This process is essentially the same as that of ignition, except for the violent decomposition of the substance being heated.

Deflagration should not be confused with **decrepitation.** This term is used to describe the behavior of certain salts, containing **interstitial water,** upon being heated. Certain compounds, of which sodium chloride is a typical example, separate from their saturated solutions without combining with water of hydration. However, as the crystals form, apparently minute quantities of the saturated solution are enclosed mechanically within the mass of the crystal. The liquid thus held is spoken of as interstitial water. If such a substance is heated, the water is changed to water vapor, which, because of the increased pressure, causes the crystals to rupture with a characteristic crackling sound closely resembling the effect produced during deflagration.

Refrigeration.—The process of cooling substances to temperatures below that of their surroundings by artificial means is known as **refrigeration.** Originally, natural ice served as the

most important source of refrigeration, but the advantages of cooling produced by mechanical means have led to the development of mechanical refrigeration on a wide scale. The chief advantages of mechanical refrigeration over that produced by natural ice are that more accurate regulation of the temperature may be obtained, lower temperatures may be reached, and the desired cooling effect is obtained at a lower cost. The development of mechanical refrigeration has had a tremendous influence upon the food industry, one aspect of which has been the creation of a new field of activity in the transportation and distribution of perishable foods in the frozen state. Closely related to this development has been the popular acceptance of mechanical refrigeration for domestic use, which has been of great significance as a health measure, not only because more efficient refrigeration serves as an added safeguard against food spoilage, but because it has induced changes in dietary habits by permitting a higher proportion of the more perishable foods, which often are of great importance because of their vitamin content, to become widely distributed and used. Another outstanding development that adds greatly to the comfort of man has been the application of refrigeration to the cooling, or so-called "air conditioning," of private and public buildings.

At the present stage of development, the refrigerating units for domestic use may be classified according to two types, usually spoken of as electric and gas refrigerators. Electric refrigeration depends upon the compression of a gas by a pump, or compressor, driven by an electric motor. Under the increased pressure, the gas liquefies and is then released by an expansion valve and allowed to vaporize in a cooling chamber. As the liquid vaporizes, heat of evaporation is absorbed from the surroundings, thus serving as a means of cooling the refrigerator. The expanded gas leaves the cooling chamber as a low-pressure vapor and is drawn into the compressor on the downstroke of the piston and expelled on the upstroke as a superheated high-pressure vapor into the condenser, which is usually provided with air circulation by means of a motor-driven fan, where the heat is discharged and the refrigerant again becomes liquid. It is again forced through the expansion valve into the cooling chamber, where the cycle is repeated. Among the liquids whose physical properties suit

them for use as refrigerants are ammonia (NH_3), carbon dioxide (CO_2), ethyl chloride (C_2H_5Cl), methyl chloride (CH_3Cl), sulfur dioxide (SO_2), and a series of chlorine and fluorine substitution products of methane or ethane known by the following trade names: Freon (CCl_2F_2), F-11 (CCl_3F), F-21 ($CHCl_2F$), and F-114 ($C_2Cl_2F_4$).

The so-called "gas refrigerator" operates upon a different principle. It depends upon the use of heat of high temperature, without the necessity of the intermediate step of converting heat into mechanical work. This type of refrigerator is known as an absorption machine and depends upon the heat from a gas flame for its source of energy, no moving parts being involved. Two substances are used that have an affinity for each other, causing them to unite, or dissolve in one another, at low temperatures; they may be separated by applying heat. As heat is applied, one of the substances is driven off as a vapor, which is condensed and allowed to re-evaporate, being absorbed by the other substance as it does so. During the evaporation of the substance, heat is absorbed from the surroundings, thus becoming effective for refrigeration.

Two kinds of absorption system are used. One of these uses water vapor, which is absorbed by sulfuric acid, while the other depends upon ammonia, which is absorbed by water. Where water vapor is used with sulfuric acid, the pressure at which the vapor is formed must be very low; hence, machines using this system are spoken of as vacuum machines. Ammonia has a much higher vapor pressure than water; hence, the system using ammonia and water may be operated at pressures above atmospheric throughout the complete cycle.

Although the basic principle of the gas refrigerator is outlined in the preceding paragraphs, the details involved in the adaptation of this principle to the self-contained gas refrigerating unit are not quite so simple as the statement of the basic principle would seem to indicate. The modern gas refrigerator utilizes at various steps in the cycle the following substances: liquid ammonia, ammonia gas, hydrogen gas, a mixture of hydrogen and ammonia gas, a strong aqueous ammonia solution, a weak aqueous ammonia solution, methyl chloride.

Ammonia gas is driven from its aqueous solution in the generator by heat from a gas flame into what is called the analyzer, where a part of the remaining water vapor is condensed, and from there to a rectifier, where the

remainder of the water vapor is condensed. From this point, the ammonia vapor is forced into the first of two ammonia condensers, where it liquefies before passing into the freezing coil, or evaporator, in which the ammonia, in the presence of hydrogen gas, evaporates, taking up heat from the surroundings. The mixture of hydrogen and ammonia gas then flows through the gas heat exchanger to the absorber, where the ammonia is absorbed by the water and the hydrogen returns through the gas heat exchanger. In the latter, an exchange of heat occurs, warming the ammonia-hydrogen mixture and cooling the returning hydrogen. The ammonia absorbed in the water returns through the liquid heat exchanger (where it cools the incoming weak aqueous solution) to the analyzer and the generator. The heat liberated in the absorber is carried away by vaporization of methyl chloride in a coil surrounding the absorber, the vapor returning to the coil after liquefaction in a condenser. The methyl chloride is contained in a closed system, which is separate from the other gases or liquids. Most refrigerators of this type depend upon air cooling, although water cooling has also been used to a limited extent.

It goes without saying that adequate means of refrigeration must be available to the pharmacist. This becomes apparent when the number of products are considered for which low-temperature storage is essential for the preservation of their therapeutic activity. Among those products which are sensitive even to moderate temperatures are the biological preparations such as the antitoxins, bacterial vaccines, blood plasma, toxoids, tuberculins, vaccines, and many glandular products including liver extract and insulin. Because of their lack of stability at higher temperatures, certain chemical compounds, notably the organic arsenic combinations such as arsphenamine, neoarsphenamine, sulfarsphenamine, and tryparsamide, must be stored at reduced temperatures. The importance of refrigeration for the biological products cannot be overestimated. Although this applies to almost all types of biological product, it is especially true of smallpox vaccine, which is said to lose its immunizing power within a few days if stored at temperatures exceeding 5°C.

Although some specific directions were given concerning the temperature of storage in the eleventh revision of the Pharmacopoeia, this list has been considerably expanded in the Pharmacopoeia XII. In addition to 11 definite classifications for which specific temperature limitations are given in the directions for storage, five other classifications are found for which limitation of heat is expressed in words, as follows: "not per-

mitted to freeze," "in a cool place," "in a cold place," "avoid exposure to excessive heat," "protected from heat and light." In the section entitled General Notices, under the subheading The Container on page 7 of the Pharmacopoeia XII, the following statements are given: "**A cold place** shall be a storage place having a temperature of not exceeding 15°C. (59°F.)." "The term **excessive heat** as used in connection with the storage of drugs shall mean a temperature above 49°C. (120.2°F.)." No definition is given in the General Notices for the term *a cool place.* It is assumed to be below 25°C., but above 15°C., which is defined as the upper limit of a cold place. The temperature of 25°C. is the standard room temperature adopted in the General Notices by the Pharmacopoeia, as indicated in the section on Temperatures, page 4, which reads as follows:

> The standard temperature for solubilities, polarimetric determinations, and for the preparation of volumetric solutions is 25°C. Unless specified in the monographs, specific gravities are given for 25°C. and refer to water at the same temperature, weighings being made in air with brass weights. For refractive indices and optical rotation measurements, temperatures other than 25°C. are directed as special conditions require.

On this same page of the General Notices a statement referring to refrigerator temperatures reads as follows: "When a refrigerator is specified for use in this Pharmacopoeia, it is intended to indicate a temperature between 2°C. and 10°C."

A tabulation of the drugs, chemicals, and preparations of the Pharmacopoeia XII for which specific directions concerning the temperatures of storage are given in the official monographs follows:

DIRECTIONS OF THE PHARMACOPOEIA XII REFERRING TO TEMPERATURES OF STORAGE

FROM −5 TO −20°C.

Citrated Normal Human Plasma (frozen)

PREFERABLY BELOW 0°C. AND NEVER ABOVE 5°C.

Smallpox Vaccine

BETWEEN 2 AND 10°C.

Antimeningococcic Serum
Antipneumococcic Serum—Type Specific
Bacterial Vaccine made from the Typhoid Bacillus
Bacterial Vaccine made from the Typhoid Bacillus and the Paratyphoid *A* and *B* Bacilli
Diphtheria Antitoxin
Diphtheria Toxin for the Schick Test
Diphtheria Toxoid
Human Immune Globulin
Human Measles Immune Serum
Human Scarlet Fever Immune Serum
Normal Human Serum
Old Tuberculin
Rabies Vaccine
Scarlet Fever Streptococcus Antitoxin
Scarlet Fever Streptococcus Toxin
Tetanus Antitoxin
Tetanus Toxoid

NOT ABOVE 10°C.

Arsphenamine

ABOVE 0°C., BUT NOT EXCEEDING 15°C.

Insulin Injection

BETWEEN 10 AND 20°C.

Citrated Normal Human Plasma (liquid)

NOT ABOVE 20°C.

Extract of Liver
Liver Injection
Neoarsphenamine
Solution of Liver
Sulfarsphenamine
Tryparsamide

NOT ABOVE 25°C.

Aromatic Syrup of Rhubarb
Compound Syrup of Sarsaparilla
Ether
Ethyl Oxide
Glycerin Suppositories
Solution of Sodium Hypochlorite
Syrup
Syrup of Citric Acid
Syrup of Glycyrrhiza
Syrup of Hydriodic Acid
Syrup of Ipecac

Syrup of Orange
Syrup of Orange Flowers
Syrup of Pine Tar
Syrup of Senna
Syrup of Tolu Balsam
Syrup of Wild Cherry
Tincture of Iodine

NOT BELOW 25°C.

Solution of Formaldehyde

NOT ABOVE 30°C.

Adhesive Plaster
Aromatic Spirit of Ammonia
Chloroform
Chloroform Liniment
Collodion
Diluted Solution of Ammonia
Ethyl Carbamate
Flexible Collodion
Hydrous Wool Fat
Pancreatin
Paraldehyde
Posterior Pituitary
Purified Benzin
Sodium Perborate
Sodium Sulfate
Spirit of Glyceryl Trinitrate
Sterile Adhesive Plaster
Thyroid
Thyroid Tablets
Wool Fat

A TEMPERATURE WHICH DOES NOT EXCEED 35°C.

Belladonna Plaster
Carbon Tetrachloride Capsules
Cerate
Magnesia Magma
Mustard Plaster
Oil of Chenopodium Capsules
Phenyl Salicylate
Solution of Hydrogen Peroxide
Solution of Iodine
Strong Solution of Iodine
Tetrachlorethylene Capsules

NOT PERMITTED TO FREEZE

Aluminum Hydroxide Gel
Magnesia Magma

IN A COOL PLACE (NOT DEFINED)

Ammonium Carbonate
Benzoated Lard
Diluted Hydriodic Acid
Ethylene
Lard
Powdered Stomach

IN A COLD PLACE (DEFINED AS A TEMPERATURE NOT EXCEEDING 15°C.)

Chloroazodin
Ephedrine
Prepared Suet
Synthetic Oleovitamin D

AVOID EXPOSURE TO EXCESSIVE HEAT
(EXCESSIVE HEAT IS DEFINED AS ABOVE 49°C.)

Camphor
Citrated Normal Human Plasma (dried)
Juniper Tar
Oil of Anise
Oil of Bitter Almond
Oil of Cedar Leaf
Oil of Chenopodium
Oil of Cinnamon
Oil of Cloves
Oil of Coriander
Oil of Juniper
Oil of Lemon
Oil of Orange
Oil of Rosemary
Peruvian Balsam
Rectified Oil of Turpentine
Tolu Balsam
Trichlorethylene
Trinitrophenol

PROTECTED FROM LIGHT AND HEAT

Ergotamine Tartrate

STUDY QUESTIONS

1. Define fusion and congelation.

2. What influence does the presence of an impurity have on the melting point of a substance?

3. Explain why a mixture of ice and water, if actively stirred, does not show a temperature above 0°C., even while being actively heated.

4. What kinds of substance are included in Class I in the description of methods for determining melting points as given by the Pharmacopoeia, and what are the essential steps of the procedure?

5. What liquid is recommended by the Pharmacopoeia for use in the bath for melting-point determinations for temperatures up to 200°C.?

6. What liquids are recommended by the Pharmacopoeia for use in the bath for melting-point determinations at temperatures above 200°C.?

7. Describe the Fisher-Johns melting-point apparatus, and explain how it is used.

8. Explain the principle involved in the use of the Dennis melting-point apparatus.

9. What kinds of substances are included in Class II as described by the Pharmacopoeia under Melting Points, and what special treatment is prescribed for the determination of the melting points of these substances?

10. Outline the procedure to be followed in determining the melting point of petrolatum.

11. Explain why a liquid that is exposed to the air and allowed to evaporate spontaneously is cooled as a result of evaporation.

12. Define heat of vaporization.

13. What is noteworthy with reference to the heat of vaporization of water as compared with the corresponding values for the other common solvents?

14. Name the five factors that influence the rate of evaporation, and explain fully what the effect of each factor is and how the effect is produced.

15. Explain why in heating a liquid it is impossible to reach a temperature above its boiling point.

16. How is the atmospheric pressure measured?

17. What is the basis for classification of the liquids whose boiling points are to be determined by Method I or Method II, according to the Pharmacopoeia?

18. What is the source of error in applying the correction in boiling points due to variation in barometric pressure prescribed by the Pharmacopoeia to nonaqueous liquids?

19. Why is the cooking of vegetables by boiling more difficult at high altitudes?

20. Define the process of desiccation, and explain the importance of this process in the preservation of freshly collected vegetable drugs.

21. List the chemical drying agents that are commonly used in desiccators.

22. What is the meaning of the term deliquescence?

23. What is the essential difference between the processes of exsiccation and desiccation?

24. What is meant by the term water of hydration?

25. Describe the process of torrefaction.

26. Name two common food products that are processed by torrefaction.

27. Define the nature of the substance treated, the conditions to be maintained, and the nature of the changes that occur in the process of carbonization.

28. What is the essential difference between ordinary charcoal and activated charcoal?

29. Why should activated charcoal for decolorizing pharmaceutical preparations be used with caution?

30. What is the nature of the substance treated and what are the chemical changes induced by the process of calcination?

31. Distinguish between incineration and ignition.

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BENTLEY, A. O. "A Textbook of Pharmaceutics," Ballière, Tindall & Cox, London, 4th ed., 1937, pp. 96–107.

COOK, E. FULLERTON, and CHARLES H. LAWALL. "Remington's Practice of Pharmacy," J. B. Lippincott Company, Philadelphia, 8th ed., 1936, pp. 109–10.

CHAPTER XI

APPLICATIONS OF AND PROCESSES INVOLVING HEAT
(Continued)

Among the pharmaceutical processes involving the application of heat remaining for consideration are distillation in its various aspects and modifications and sublimation. Distillation is one of the most ancient processes known. According to Wootton[1] there is evidence to indicate that distillation was known to the Chinese in the most remote periods of their history; and possibly it was used by them for the distillation of wine. Berthelot investigated some alleged early references and arrived at this conclusion. Aristotle mentions the possibility of rendering sea water potable by vaporizing it. At Alexandria, in the first century of the Christian era, it is known that condensing apparatus was invented and used, but no reference to the distillation of wine is found in any of the writings of that period. Nicander is the earliest authority to refer to the products of distillation (about 140 B.C.). He mentions water distilled from roses and uses the Greek word *ambix* as the name for the apparatus employed in the process. It was this word which, when adopted by the Arabs and prefixed by their article *al*, became *al-inbiq*, which in turn was Anglicized to become the word **alembic (limbeck).** Originally, this meant a cup-shaped vessel that was set on or near a fire, but gradually it came to mean a type of still having the condenser mounted vertically above the boiler.

Distillation.—In its simplest form, distillation is the process of vaporizing a liquid and recovering it by cooling and condensing the vapor. The apparatus required for simple distillation consists essentially of three objects: a **boiler,** or vessel, in which the vapors are produced by heating the liquid to its boiling point; a **condenser,** which provides for the cooling of the vapors either by the circulation of water or by the use of air at atmospheric tem-

[1] A. C. WOOTTON. "Chronicles of Pharmacy," Macmillan & Company, Ltd., London, 1910, Vol. I, p. 327.

perature; and a **receiver** provided for the collection of the condensed liquid. The process may have as its object the separation of a liquid from a solid dissolved in it, the separation of a volatile liquid from one less volatile, or the decomposition of organic substances by the effect of heat and the condensation of the volatile vapors that are given off.

Stills.—The apparatus used for the generation of vapors is called the still, though the term is frequently used to indicate the boiler and condenser collectively. The device first used for distillation was the alembic, which, as previously indicated, was an apparatus in which the condenser, usually air-cooled, was placed above the boiler. Although this arrangement is still used to a limited extent in certain modern types of still, it is less efficient

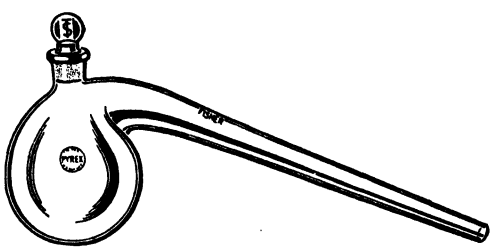
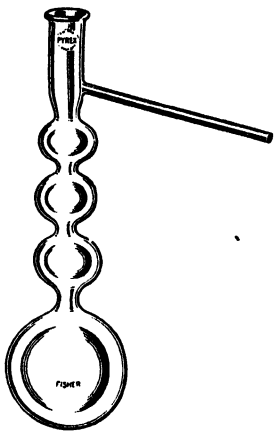


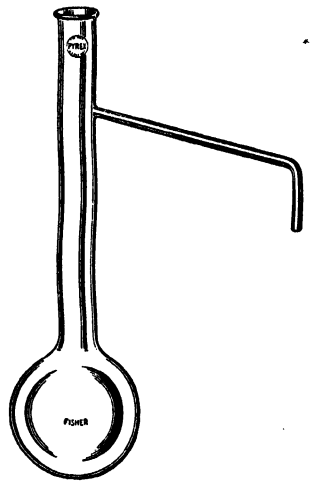
FIG. 74.—The retort.

than stills employing the retort principle because of the heat that is transmitted by conduction and radiation to the condensing surface from the boiler.

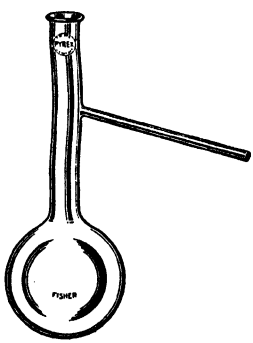
With the increased use of the process of distillation, another type of still came into use. This was called a **retort,** a term derived from its bent shape (from the Latin *retortus,* turned back), and consisted of a bulb having a long tapered neck attached at a sharp angle. As can be seen from Fig. 74, the retort combined the functions of the boiler and the condenser in one unit. The long neck of the retort was cooled by the atmosphere. Retorts are manufactured in two varieties, plain and tubulated. As can be seen from Fig. 74, the tubulated retort is provided with an orifice in the bulb for greater convenience in introducing the liquid to be distilled. Retorts made from glass, porcelain, earthenware, fused silica, platinum, iron, copper, lead, etc., may be obtained, according to the special purposes for which they are intended. Porcelain and earthenware retorts are used in the



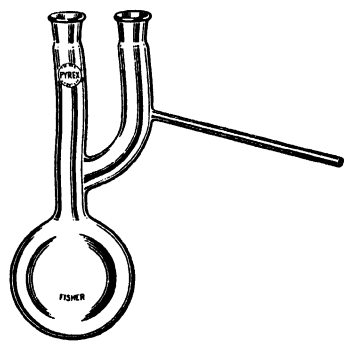
Ladenburg type.



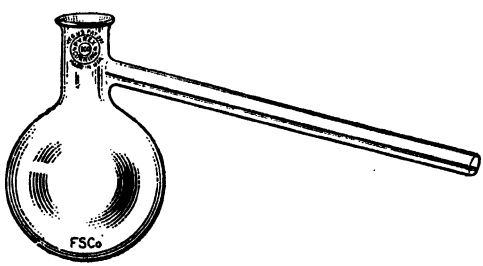
Hempel type.



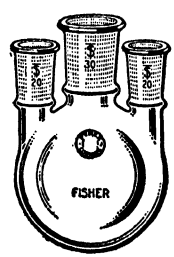
Plain type.



Claissen type.



A.S.T.M. type.



Three-neck type.

FIG. 75.—Distilling flasks.

distillation of phosphorus and mercury. Platinum and iron retorts are used in destructive distillation. Lead retorts are used in the manufacture of hydrochloric acid and ether. Except for these special uses, the retort has, for the most part, been replaced by the modern distilling flask. These come in a variety of styles, shown in Fig. 75.

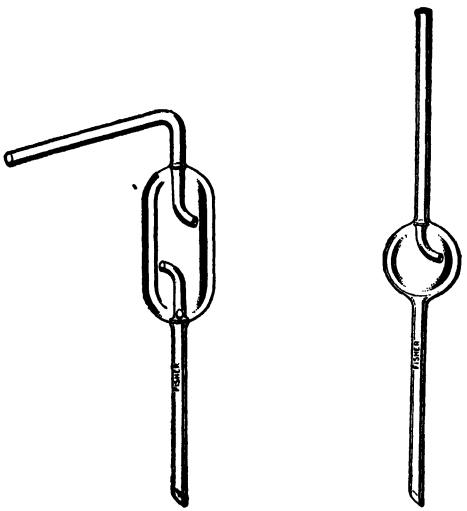
Bumping.—Many liquids, especially when heated in vessels having smooth inner surfaces, are subject to the phenomenon of **superheating.** A liquid may commence to boil smoothly, with a steady stream of bubbles rising to the surface, when suddenly the boiling stops momentarily and a violent burst of vapor occurs. This may exert sufficient force to cause the flask to rise slightly from its support or, in extreme cases, to burst. This behavior is spoken of as "bumping" and is the source of considerable difficulty in many distillations.

It has been observed that this tendency is more pronounced when a liquid is boiled in a vessel with smooth surfaces. For this reason, solid objects, such as pieces of unglazed porcelain, pumice stone, glass beads, or capillary tubes sealed in the middle, are frequently added; the latter are effective both in ordinary and in vacuum distillation. The rough surfaces and angular points of these objects serve as nuclei for the formation of bubbles of vapor. For the best effect, these should be added before heating is started.

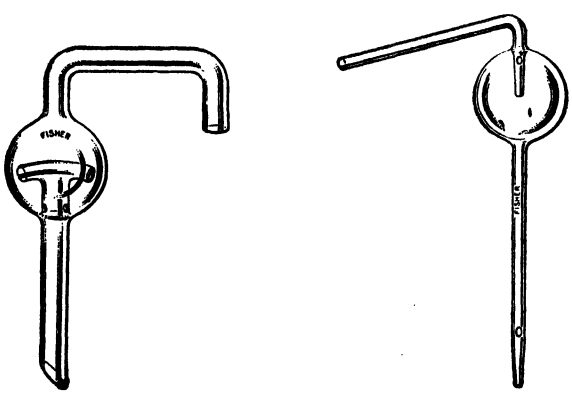
A more effective method for overcoming bumping is available when distillation under reduced pressure is being conducted. It is possible under these conditions to take advantage of the partial vacuum in the distilling flask by inserting a long tube drawn to a fine capillary, which emits a constant stream of air bubbles near the bottom of the flask, the air being drawn from outside the flask by the partial vacuum maintained throughout the distillation. Unfortunately, this procedure is feasible only in distilling under reduced pressure. However, for distillations carried out at atmospheric pressure, if air under pressure is available equally good results may be obtained by using a current of air bubbles forced through the boiling liquid.

In some cases where bumping is persistent, there is danger of some of the liquid in the distilling flask being carried over mechanically by the rapid evolution of vapors. This behavior

is sometimes spoken of as **entrainment.** If this should occur, the distillate becomes contaminated with the less pure liquid contained in the distilling flask and the purpose of the process is



Kjeldahl types.



McHargue type. Hopkins type.

FIG. 76.—Connecting-bulb distilling traps.

defeated. Guarding against this possibility is especially important in the distillation carried out as a part of the Kjeldahl method for the determination of nitrogen. As one step in this process, the nitrogen is converted into an ammonium salt, and

at this point the liquid is made strongly alkaline by the addition of an excess of sodium hydroxide to the distilling flask. Under these conditions, ammonia gas is liberated and distilled over in the presence of water vapor and received in a measured volume of a previously standardized solution of an acid (a volumetric solution). By residual titration of the excess acid in the receiving flask, with a standardized solution of base, the exact quantity of nitrogen in the original sample may be calculated. Under the conditions of this determination, if only a single drop of the strongly alkaline solution in the distilling flask (containing the nonvolatile sodium hydroxide) were to be carried over mechanically to the receiver, the accuracy of the determination would be completely destroyed. Protection against this contingency in this and similar distillation processes may be secured by the use of distilling traps installed between the distilling flask and the condenser. Various styles are shown in Fig. 76. Some are designed for use in a vertical position, while others are intended to be connected with the side arm of the flask and the condenser at a slight angle below the horizontal.

Frothing.—In the distillation of certain liquids, difficulty is sometimes encountered because of the frothing that occurs as the liquid begins to boil. This tendency is more pronounced in alkaline liquids or those containing soaps, saponins, mucilages, albumens, or gums. Various methods have been suggested for overcoming or reducing this difficulty; many of these are of some value, although none has been found that eliminates frothing entirely. It has frequently been observed that a small amount of mineral oil, melted paraffin, or white or yellow wax added to the contents of the flask serves to reduce the amount of frothing. Occasionally, it is possible to acidulate an alkaline solution by the addition of an excess of phosphoric or sulfuric acid. In other cases, the addition of a solution of calcium chloride is found to be helpful.

In some instances, despite whatever remedial measures may have been taken, frothing may persist to an annoying degree. In such cases it is recommended that a distilling flask should be selected having sufficient capacity to hold several times the volume of liquid to be distilled, in order to provide additional space for the froth that is formed. A distilling trap should also

be used as a further precaution. In most cases where difficulty due to frothing occurs, it is found that this tendency is more pronounced at the beginning of the process and tends to decrease gradually as the distillation progresses.

Condensation.—Distillation consists of two steps, **evaporation** and **condensation.** The theoretical aspects of evaporation were considered in Chap. X. Condensation is the reverse of the process of evaporation or vaporization. It will be recalled that, in order that 1 Gm. of water at 100°C. may be converted into water vapor (at normal atmospheric pressure) of the same temperature, the expenditure of 537 cal. of heat energy is required. Accordingly, when water vapor is condensed by cooling, this same quantity of heat (the latent heat of vaporization) is liberated. Unless adequate provision is made to carry away the heat that is released, the condenser soon becomes too hot to condense the vapor at all and permits it to escape into the atmosphere.

It is fortunate that most of the liquids used in pharmaceutical preparations have much lower heats of vaporization than that of water. Table XIX (page 289) shows that the corresponding value for benzene is 94.3 cal.; for chloroform, 59 cal.; for ether, 83.9 cal.; and for alcohol, 204 cal. Thus, it can be seen that the problem of removing the heat liberated upon condensation of the vapors of these liquids is appreciably less difficult than is the case with water vapor. The condensation of water vapor requires a more rapid heat exchange than that required for any of the other vapors produced from the common solvents used in pharmaceutical preparations. According to Cook and LaWall,[1] it has been calculated that steam at 100°C. requires about twenty-five times its weight of water at 20°C. to condense it. Although many liquids possessing relatively low heats of vaporization may be condensed successfully in an air condenser, *i.e.*, a tube of glass, such as the side arm of a retort, exposed to the cooling effect of the air at ordinary room temperatures, the slow rate of heat transfer by this method makes it unsuitable for use in the distillation of aqueous liquids. In such cases, water is used as the cooling medium and is most effective when supplied as a stream from a

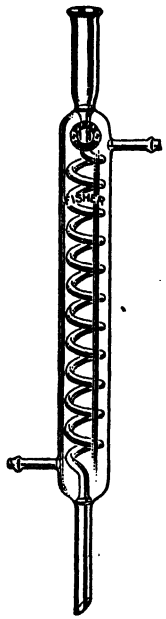
[1] E. F. Cook and Charles H. LaWall. "Remington's Practice of Pharmacy," J. B. Lippincott Company, Philadelphia, 8th ed, 1936, p. 133.

constant source, rather than when used by simply surrounding the condensing tube with a relatively large volume of water that is not in motion. The constant motion provides for the continuous replacement of the water as it becomes heated.

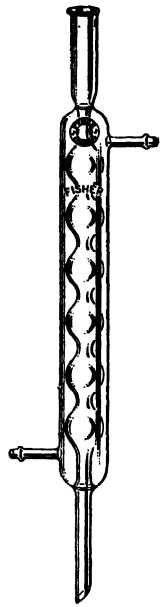
In addition to providing for adequate cooling, the efficiency of a condenser depends on its design and construction and the way in which it is used. It is important for the condenser tube to be constructed so that it may be easily cleaned, in order to avoid contaminating the product of one distillation with that of a previous one. The condenser should be designed so as to have a relatively large cooling surface, since the rate of condensation is proportional to the area of surface exposed. The condensing surface should be made of a substance which is a reasonably good conductor of heat, for the rapidity of condensation is proportional to the speed with which the heat is carried away. For this reason, metallic condensers are more efficient than those made of glass, although frequently the nature of the liquid being distilled precludes the use of the former, because of the danger of chemical reactions. For best results, the film of liquid that forms on the surface of the condenser tube should be removed as rapidly as formed, since, in most cases, the condensed liquid is a relatively less efficient conductor of heat than the glass or metal of the condenser tube. The adjustment of the angle of the condenser to secure rapid flow of the distillate from the condenser is helpful in this connection. Finally, the direction of flow of the cooling water should be opposite to that of the flow of vapors to be condensed. (This does not apply to the use of reflux condensers.) Not only does this provide for keeping the cooling chamber surrounding the condenser tube completely filled with water, since the water is admitted at the lower orifice, but it ensures more complete condensation because the vapors travel down the condenser from the warmer to the cooler portions of the tube.

Condensers.—Condensers are available in various forms and designs, for the most part representing modifications of the original Liebig condenser, which consists of a straight condensing tube surrounded by a cooling chamber. A number of types of condenser are shown in Fig. 77. The Liebig condenser may be obtained with the condensing tube and the cooling jacket as

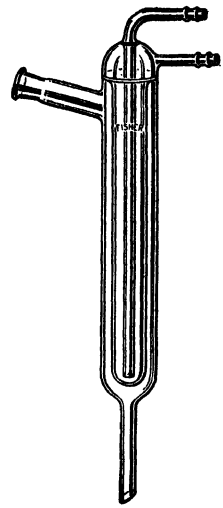
Liebig type.



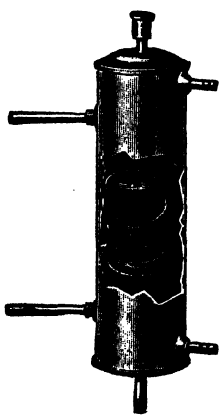
Graham worm type.



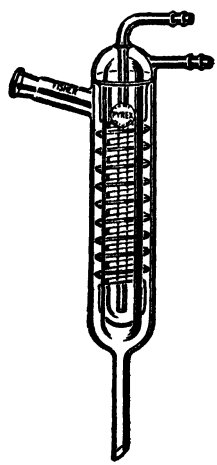
Allihn reflux type.



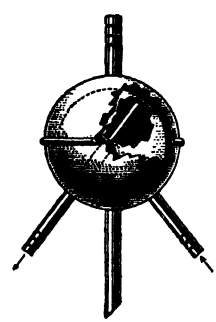
Hopkins reflux type.



Hallock block-tin coil type.



Friedrichs type.



Soxhlet type.

FIG. 77.—Condensers.

separate units, to be assembled by means of rubber or bakelite threaded connections or rubber stoppers. These have the advantage of permitting a replacement of parts in case only the jacket or the condensing tube is broken. The original Liebig condenser was assembled as a single unit, the cooling jacket being sealed to the condensing tube; they may still be obtained in this form, especially if made of pyrex glass. It is also possible to secure brass jackets to replace the glass cooling jacket, which greatly reduces the danger of breakage. The **worm condenser** is a particularly efficient type of condenser, since it offers a much greater cooling surface in proportion to its length than does the straight Liebig condenser. It requires a vertical mounting in use, since otherwise the condensed liquid collects in the lower portions of the convolutions of the tube and, as the vapor enters the condenser, the pressure of the vapor causes the distillate to spurt out from it. At the same time, a certain amount of back pressure is produced by the presence of the liquid retained in the condenser worm, and this interrupts the smooth progress of the distillation process. Condenser tubing made of such materials as copper, brass, or iron are little used for distillations because of their tendency to react chemically with most liquids. On the other hand, block tin has little solubility in water or the common solvents and is frequently used in the condenser tubes of stills used to produce distilled water. The Hallock block-tin coil condenser is an example of this type.

In some instances, the object of distillation is not to separate a liquid from a dissolved substance, or one liquid from another, but to permit the use of heat in the digestion or extraction of a substance with a volatile solvent, such as alcohol, ether, or chloroform, at the boiling point of the solvent, and, at the same time, prevent loss of the solvent by evaporation. If the material to be digested or extracted is placed in contact with the solvent and heated in an open container, the volatile solvent is soon completely driven off. In order to prevent this, **reflux** (or return-flow) **condensers** are used. These are mounted in a vertical position in the neck of the flask containing the material being treated. As vaporization occurs, the volatile solvent is condensed and flows back into the extraction flask. The Hopkins and the Allihn reflux condensers are especially designed for

this use. It will be noted that the condenser tube of the Allihn condenser contains a series of bulbs for the purpose of increasing the condensing surface and hence securing greater efficiency. The Hopkins reflux condenser employs a somewhat different principle in that the cooling chamber is contained inside the condensing tube. The cooling water is admitted at the upper tube; this extends to the bottom of the cooling compartment, from which it flows upward to the exit tube, also located near the top of the condenser. The side arm is ordinarily left open for extractions carried out at atmospheric pressure. If for any reason it is desirable to carry out the extraction under reduced pressure, which has the effect of lowering the boiling point of the solvent, a water pump or mechanical pump may be attached at this point to reduce the pressure.

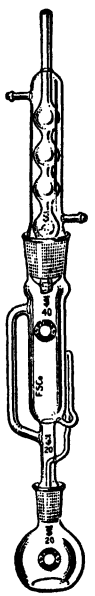
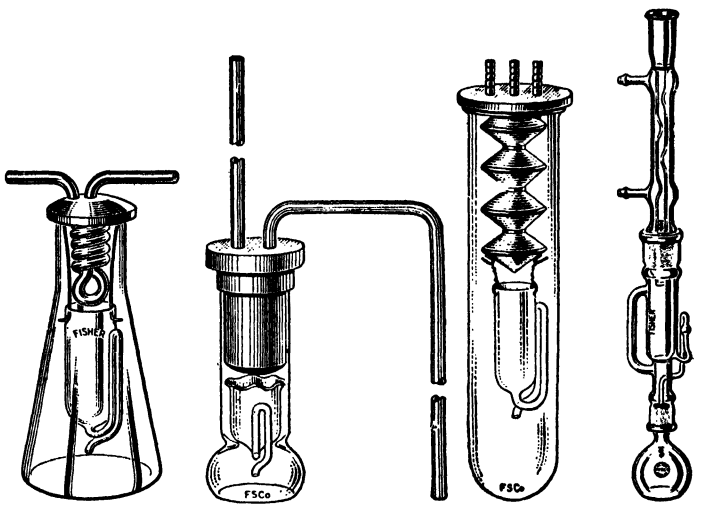


FIG. 78.—Soxhlet extraction apparatus.

In connection with the use of volatile solvents for the extraction of animal and vegetable drugs, the Soxhlet extraction apparatus is widely employed. It has the advantage of requiring only a limited amount of solvent, which is used repeatedly by being purified by redistillation following each passage through the drug. The apparatus is shown in Fig. 78. The material to be extracted is placed in a thimble, made of thick, bibulous paper, in the extractor, which is the central unit shown in Fig. 78. The solvent is placed in the distilling flask attached to the base of the extractor and subjected to heat. As the volatile liquid boils, the vapors rise and travel upward by means of the larger side tube to the condenser, which is mounted above the extractor. As the vapors condense, the liquid drops into the extraction chamber, passing through the drug contained in the extraction thimble. The solvent continues to rise until the level of the liquid just exceeds the level of the bend in the small siphon tube shown at the side of the extraction chamber. At this point, the siphon is automatically primed, and all the liquid is ultimately drained back into the distilling flask. As the liquid is redistilled, the extracted material is accumulated in the distilling flask and the

drug is repeatedly extracted with the pure solvent. The process is continued until the extraction is complete. In this way, a very small volume of solvent serves to extract all the soluble material in the drug.

In addition to the Soxhlet apparatus, a number of other types of extractor have been devised for continuous extraction with volatile solvents. Some of these are shown in Fig. 79. The



A.S.T.M. type. Bailey-Walker type. Wiley type. Soxhlet micro-extractor.

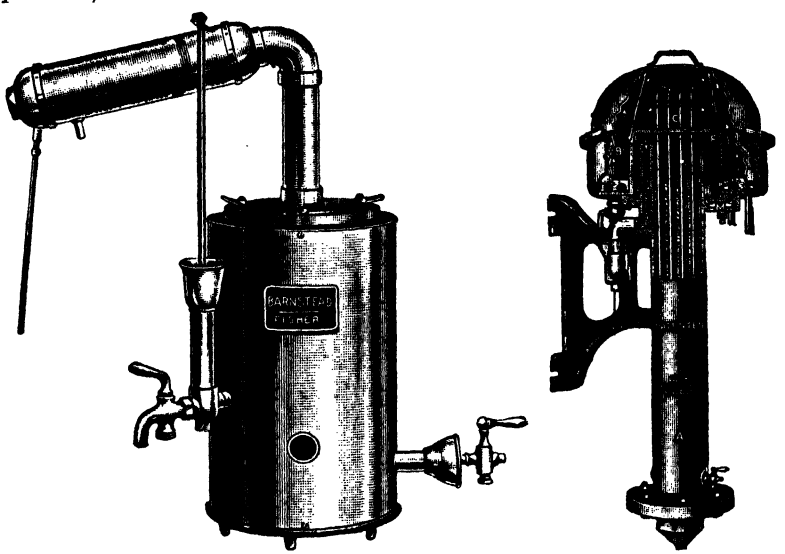
FIG. 79.—Continuous-extraction apparatus.

principle applied in their operation is the same as that for the Soxhlet apparatus already described and involves the redistillation of the solvent, which is permitted to percolate through the sample as it is collected from the condenser.

The types of still and condenser which have been described here are those which would normally be used in ordinary laboratory experiments. Special stills have been devised for large-scale operations in the production of distilled water and the distillation of alcohol and of petroleum products, which are not considered here because of lack of space. Some of these are highly ingenious in their design and construction. Stills for the production of distilled water have been devised that are completely automatic and operate continuously, maintaining a constant supply of water

in the boiler and producing distilled water at a uniform rate. For special information on stills of this type, it is suggested that the references listed at the end of this chapter should be consulted.

Distilled Water.—The preparation of pure water by the process of distillation is of great importance in pharmacy. Water is never found in the absolutely pure state in nature. It usually contains salts and other mineral substances, together with traces of organic matter and decomposition products, some of which are volatile and others are nonvolatile. The



Barnstead. Stokes.

FIG. 80.—Water stills.

separation of water from the nonvolatile material is easily accomplished by distillation. The complete removal of the volatile material is considerably more difficult. Experience has shown that the volatile constituents tend, because of their high volatility, to pass over with the first portions of the water being distilled. Accordingly, it has become the practice to reject the first portion, varying from a tenth to a fifth of the total volume being distilled, in the hope of eliminating the majority of these volatile constituents. It has also been found practical to stop the process of distillation at a point where approximately the same proportion as that rejected remains in the still. The object of this procedure is to prevent the decomposition of the nonvolatile substances by prolonged heating, which might otherwise give rise to traces of volatile material. Such a process was official in the ninth revision of the Pharmacopoeia.

The National Formulary VII lists a form of water known as Redistilled Water (Aqua Redestillata), which is also known as Double-distilled Water.

This is described as water that contains not more than negligible amounts of oxidizable matter, nonvolatile matter, or gases. The procedure for the preparation of redistilled water may be summarized as follows:

Distilled water is placed in a distillation flask of resistant glass, which is connected to a suitable glass container by means of a ground-glass joint. Ten cubic centimeters of potassium permanganate test solution and 5 cc. of sodium hydroxide test solution are added to each liter of water. The

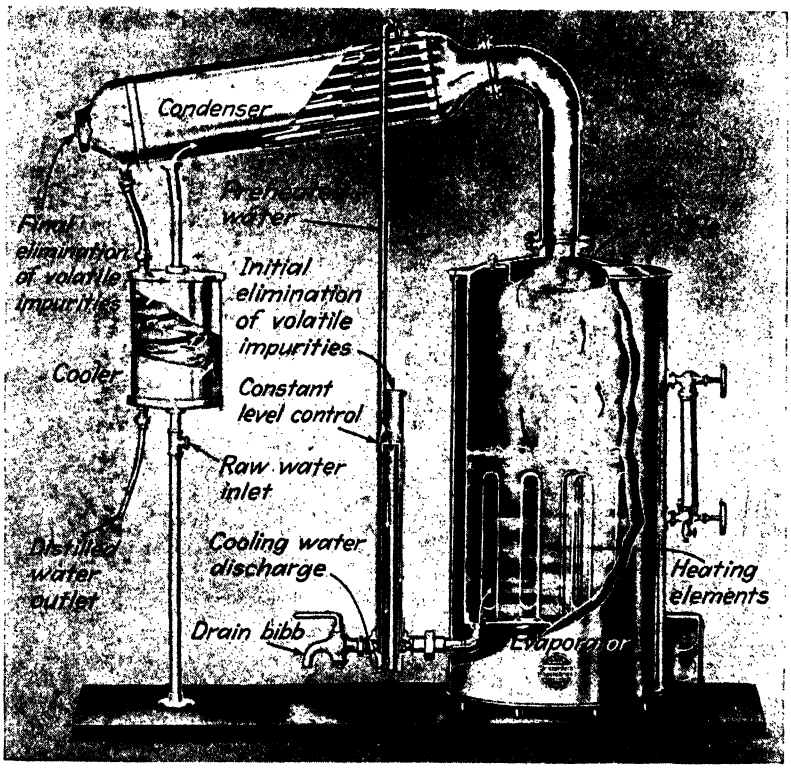


FIG. 81.—Sectional view of Barnstead water still.

object of this treatment is to oxidize insofar as possible the organic material that may be present, and to convert any free acids, if present, into the nonvolatile sodium salts. The distillation process is started by boiling gently to avoid entrainment, and the distillate is collected in tall 50-cc. Nessler tubes. As soon as each tube is filled to the mark, 2 cc. of alkaline mercuric potassium iodide test solution is added. This reagent produces a yellowish color in the liquid if it contains appreciable quantities of ammonia. The distillation is continued, the distillate being collected in 50-cc. portions and tested as before, until the last portion tested fails to show any yellowish

discoloration. At this point, it is assumed that the distillate is free from ammonia, and the distillation is continued, the distillate being collected in 500-cc. sterile flasks.

When approximately one-tenth the original distilled water remains in the distillation flask, the collection of distillate is halted. If a gas flame is used as a source for heat during the process, care must be exercised to avoid the absorption of the products of combustion of the gases by the distillate. Further, the process must be carried out aseptically so that the redistilled water will not be contaminated with microorganisms. The extreme care required in the preparation of redistilled water is justified because of the fact that this product is used in the preparation of sterile parenteral solutions intended for hypodermic, intravenous, or intramuscular administration.

Distillation under Reduced Pressure.—Although it has been shown that evaporation takes place from the surface of liquids at any temperature, the rate depending mainly on the vapor pressure of the liquid at the existing temperature, it is apparent that the maximum rate of evaporation will be attained only when the liquid is actively boiling. Therefore, from the standpoint of efficiency, it is desirable for distillation to be carried out at the boiling point of the liquid.

However, numerous organic liquids with high boiling points are known, such as glycerin and the volatile oils, that tend to decompose at temperatures near their boiling points. If an aqueous solution of sugar is concentrated by boiling the solution, the brown color of molasses is developed and the sugar that is recovered is dark brown in color. This is because the sugar is partly changed chemically at the temperature required to evaporate the water at the boiling point of the solution, owing to caramelization.

Another example of instability in respect to heat that has a closer connection with pharmacy is encountered in the manufacture of extracts and fluidextracts from vegetable drugs. In both classes of preparation, it is necessary to remove the excess of solvent or menstruum (usually a mixture of alcohol and water) in order to obtain a higher concentration of the active principles of the drug. Yet in many cases the prolonged exposure of the extractive to the heat necessary to accomplish this purpose brings about a partial decomposition and seriously impairs the therapeutic usefulness of the resulting product. In the general monograph

on Extracts, page 174 of the twelfth revision of the Pharmacopoeia, the following statement appears: "If the active principles are damaged by high temperatures or prolonged heating, the temperature at which its percolate is concentrated is not to exceed 60°C. at any stage." In the general monograph on Fluidextracts, which appears on page 187, the directions for the preparation of fluidextracts by type processes *A* and *B* specifically require that the weak percolate shall be concentrated to a soft extract at a temperature "not exceeding 60°C." Since the

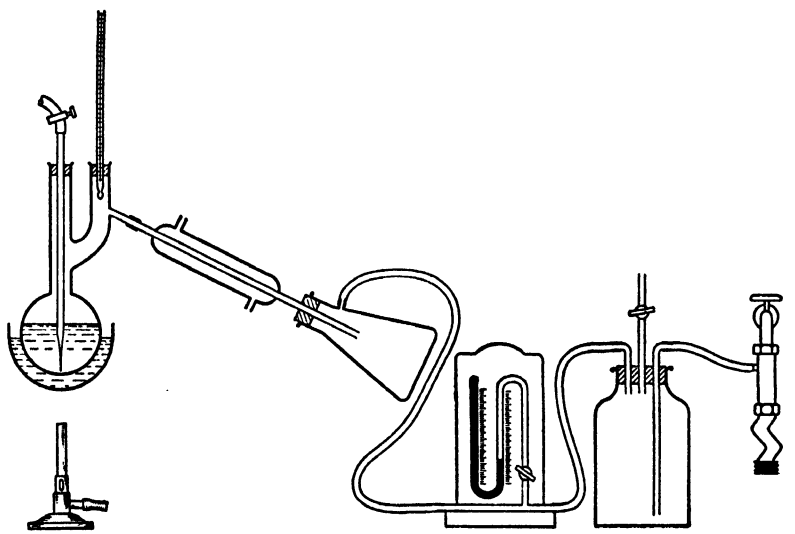


FIG. 82.—Distillation under reduced pressure.

boiling point of pure alcohol is 78°C. and the menstruums used in the preparation of extracts and fluidextracts always contain some water, either added in the original menstruums or extracted from the moisture contained in the drug, it is apparent that evaporation or distillation under the usual conditions of pressure will not serve. The solution to such problems lies in **distillation under reduced pressure,** or so-called **vacuum distillation.**

It will be recalled that, in the discussion of evaporation in Chap. X, it was pointed out that the pressure on the surface of a liquid is one of the factors influencing the rate of evaporation. It was also pointed out in the discussion of steam baths in Chap. IX

that a liquid boils at the point when its vapor pressure overcomes the opposing atmospheric pressure. Hence, if distillation is carried out in a closed system, provided with a suitable means of diminishing the pressure in the system, it is possible to adjust the boiling temperature of the liquid (within certain limitations) to any desired level. In this way, the deleterious effects of excessive heat may be avoided without retarding the process of distillation in any way.

Some conception of the effects of changing pressure on the boiling point of liquids may be obtained from Table XX, which lists the vapor pressure of water at various temperatures.

TABLE XX.—THE BOILING POINT OF WATER AT VARIOUS PRESSURES[1]

Temperature, °C.	Pressure, mm. of mercury	Temperature, °C.	Pressure, mm. of mercury	Temperature, °C.	Pressure, mm. of mercury
0	4.579	35	42.175	70	233.7
5	6.543	40	55.324	75	289.1
10	9.209	45	71.88	80	355.1
15	12.788	50	92.51	85	433.6
20	17.535	55	118.04	90	525.76
25	23.756	60	149.38	95	633.90
30	31.824	65	187.54	100	760.00

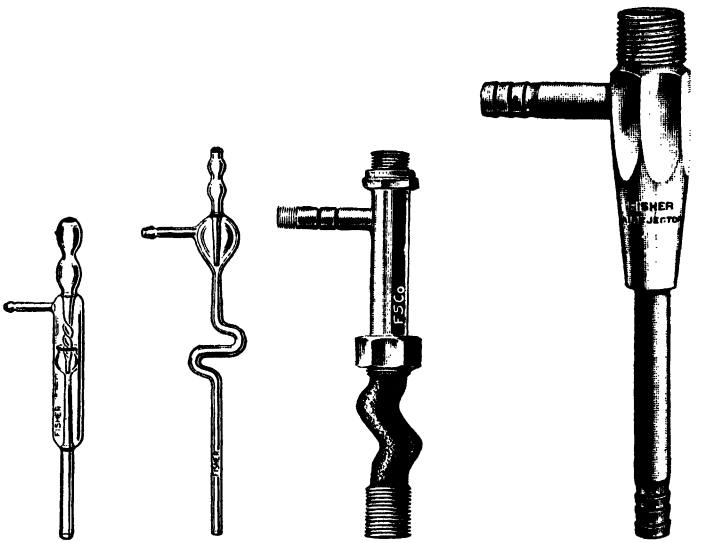
[1] Selected from a table appearing in N. A. Lange, "Handbook of Chemistry," Handbook Publishers, Inc., Sandusky, Ohio, 2d ed., 1937, p. 1203.

Although the table from which these data were taken is intended to show the vapor pressure of water at various temperatures, it must be remembered that any liquid boils whenever its vapor pressure equals the pressure on its surface, which means that, if the pressure on a given liquid is reduced, at a given temperature, to a point just equal to the vapor pressure of that liquid at that temperature, the liquid will boil.

In order to carry out distillation under reduced pressure, a suitable pump must be provided, together with a vacuum flask, to serve as a receiver. A manometer gauge is a useful adjunct for measuring the pressure, and a thermometer should also be employed to indicate the temperature of the boiling liquid. The use of a tube drawn to a fine capillary to admit a stream of air

bubbles near the bottom of the distilling flask to prevent bumping is also recommended.

The type of air pump known as the **aspirator** or **water pump** is well suited for ordinary distillations at reduced pressure, in which extremely low pressures are not required. Several styles are shown in Fig. 83. They are made of glass or metal and are operated by attaching to the water line and passing a rapid stream of water through them. As can be seen in the figures for



Muencke swirling type. Geissler type. Richards type. Airejector type.

FIG. 83.—Aspirators or filter pumps.

those made of glass, the stream is made to pass at high velocity through a constriction in the tube and as the water emerges from the nozzle, air that is drawn in from the side arm is beaten into a foam and carried out mechanically. The purpose of the irregular course of the outlet tube in some of the types shown is to increase the turbulence and to prevent the air contained in the foam from separating and returning to the partly evacuated system. Devices of this type are remarkably efficient for ordinary operations but are unsuited for high-vacuum work, because the absolute minimum of pressure which can be attained even under ideal conditions is limited to the vapor pressure of

water at the temperature at which it is used. Reference to Table XX shows that this value approximates 24 mm. of mercury at 25°C., or 18 mm. at 20°C.

For distillations requiring lower pressures, it is necessary to use a mechanically operated air pump, such as that shown in Fig. 84, which is driven by an electric motor and may be used

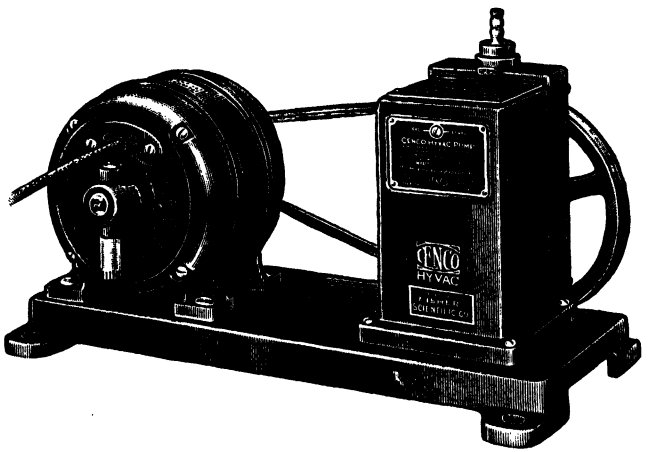


FIG. 84.—Vacuum pump.

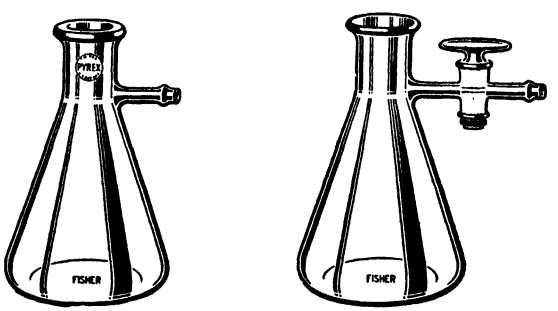


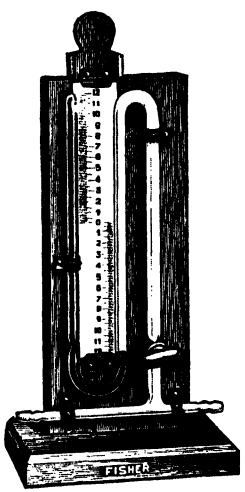
FIG. 85.—Vacuum flasks.

for either pressure or vacuum. The pump is of the rotary-piston type and is oil sealed. It is capable of producing a vacuum corresponding to 0.1 mm. of mercury. Still more efficient pumps of this type are available, some of which will produce a vacuum corresponding to 0.0001 mm. of mercury.

The suction flasks used as receivers are made of thick glass designed to withstand the external pressure as the air is partly

exhausted. Two forms are shown in Fig. 85. The type having the stopcock in the side arm is particularly useful as a means of preventing backflow of water from the water pump into the receiving flask, after the pump is shut off. Otherwise, it is necessary for the system to be vented, before turning off the pump, or for a water trap to be used in order to prevent backflow.

The instrument used to measure the pressure is called a manometer and in its simplest form closely resembles the Torri-



Vacuum manometer, improved Bennert type.

Manometer for pressure or vacuum.

FIG. 86.—Manometers.

cellian tube. If a U tube, open at both ends, is partly filled with mercury, it may be used to measure either pressure or vacuum. Two commonly used types of manometer are shown in Fig. 86.

The use of such apparatus as has been described is chiefly for small-scale operations, and principally where the object is to purify a liquid substance by distillation and at the same time protect it from the effect of high temperatures. It is obvious that glass distilling flasks are unsuitable for use in the large-scale preparation of solid extracts because of the difficulty of removing the solid residue from the flask at the end of the process. For

such purposes, special apparatus, known as *vacuum stills* or *vacuum pans*, are provided, some of which have capacities amounting to hundreds of gallons. They are usually made in the form of a large sphere, or they may be ovoid in shape, and are separated at the center into two halves fitted together to form an airtight connection by means of a gasket and suitable screw clamps. Such stills are usually made of brass, contain steam coils for heating, and may be lined with glass or porcelain. Equipment of this sort is widely used in pharmaceutical manufacturing.

Fractional Distillation.—The object of the process of **fractional distillation** is to effect a more or less complete separation of two or more liquids that differ from one another in their degrees of volatility. The boiling point (Chap. X, page 294) of a single liquid (*i.e.*, a chemical entity) is that temperature at which the vapor pressure is equal to the external pressure, and the same rule holds for mixtures of liquids. However, there is no general rule by which the vapor pressures of mixtures may be computed from the known vapor pressures of the components of a mixture, nor is it possible in all cases to predict the boiling point of mixtures directly from the vapor pressures alone. This is because other factors enter into the problem, such as the solubility or lack of solubility of the components, one in the other, and the individual behavior of certain liquids or combinations of liquids. These factors do not permit broad generalizations to be drawn. For the most part, we are dependent on a study of the physical behavior of the particular liquids in question and on the observations that have been made experimentally of these particular mixtures.

In general, the types of mixtures of two or more liquid components may consist of the following:

1. Liquids that are insoluble in each other.
2. Liquids that are miscible in all proportions.
3. Liquids that have only a limited solubility in each other.

With reference to mixtures of liquids that are insoluble in each other, the separation of such mixtures may frequently be effected by purely physical methods, such as the use of the separatory funnel or by siphoning off the supernatant layer, thus avoiding the necessity of resorting to the more laborious and time-consuming process of fractional distillation (see Chap. XVIII,

page 518). This particular type of mixture is encountered in the steam distillation of the volatile oils from plant materials. The theoretical aspects of the behavior of immiscible liquids will be discussed more extensively under Steam Distillation (page 350). It is sufficient to point out here that the vapor pressure of the mixture, at any given temperature, is equal to the sum of the vapor pressures of the components for that same temperature and that ebullition occurs whenever the total vapor pressure equals the external pressure.

Mixtures of liquids of the third class, namely, mixtures consisting of liquids having only a limited solubility in each other, show characteristics that are in part similar to those of immiscible liquids; at the same time, insofar as the limit of solubility permits, they reflect the behavior of liquids that are miscible with each other.

Fractional Distillation of Miscible Liquids.—The most important application of fractional distillation has as its object the separation of two or more liquids that are soluble in all proportions in each other, and we shall confine our discussion to mixtures of this type. Even with miscible liquids, we are dependent on experimental observations of the boiling points and the compositions of the vapor mixtures at various boiling-point temperatures. The management of the process and the degree of separation that results are therefore influenced to a large extent by the characteristic behavior of the particular mixture of liquids in question.

Experimental evidence has shown that for binary mixtures (containing two components) the behavior of various mixtures of miscible liquids falls into one of three categories:

CLASS I.—The boiling point of the mixture changes uniformly with the composition of the mixture in the distilling flask and is always lower than the boiling point of the less volatile constituent but greater than that of the more volatile component.

CLASS II.—The boiling point changes with the composition of the mixture in the distilling flask but at one particular composition attains a maximum greater than that of the less volatile constituent.

CLASS III.—The boiling point changes with the composition of the mixture but at one particular composition attains a minimum value less than that of the more volatile component.

In mixtures of Class I, the boiling point is determined by the original composition of the mixture and is always lower than the boiling point of the less volatile constituent. Since the more volatile component vaporizes more rapidly than the less volatile constituent, the percentage of the more volatile component in the mixture constantly decreases. As a result, the boiling point will gradually rise until finally it reaches the boiling point of the less volatile constituent. Examples of mixtures that exhibit this behavior are the following: benzene and toluene, methanol and water, acetic acid and water.

Mixtures of miscible liquids of Class II exhibit an anomaly in the composition curve with a change in the boiling point of the mixture in that, at one particular composition, a maximum boiling point is reached which is greater than the boiling point of either of the components. This means that, at this maximum temperature, the composition of the distillate will be identical with that of the mixture in the distilling flask. Such a mixture is spoken of as a *constant boiling mixture*. It was formerly regarded as a chemical combination, but evidence shows that it exhibits a constant boiling point only at a constant pressure and that, if the external pressure is increased or decreased, the boiling point of the mixture changes. The behavior of mixtures of Class II may be interpreted to mean that, if the original composition of the mixture varies from that of the constant boiling mixture and contains a higher proportion of the more volatile constituent, the latter will be distilled off at a more rapid rate, resulting in a corresponding increase in the boiling point of the mixture until the proportion of the two components is adjusted to that of the constant boiling mixture, whereupon the boiling point of the mixture remains constant. On the other hand, if the composition of the mixture is such that its initial boiling point is less than the maximum attained by the constant boiling mixture, owing to the presence of too high a proportion of the less volatile constituent, then the less volatile constituent will distil at a more rapid rate until the proportion is reduced to that required for the constant boiling mixture, the boiling point again attaining a maximum value. Mixtures of nitric acid and water and of hydrochloric acid and water exhibit this behavior when distilled together, as do mixtures of formic, hydrobromic, hydri-

odic, hydrofluoric, and perchloric acids with water. Acetone (b.p. 56°C.) and chloroform (b.p. 61°C.) form a constant boiling mixture that boils at 64.7°C. The formation of constant boiling mixtures is of importance in the commercial production of the acids in that they may be used for preparing acid solutions of predetermined strength, since the composition of such mixtures is known and remains constant with constant pressure.

Mixtures of Class III exhibit a similar anomaly in their composition curve; but, in this case, the temperature of the constant boiling mixture is below that of either of the constituents. Among the mixtures that show this behavior are alcohol and water and isopropyl alcohol and water. Whenever any substance is dissolved in a liquid, the boiling point of the liquid is raised. This is accounted for by the fact that the vapor pressure is lowered and, accordingly, a higher temperature is required to increase the vapor pressure to that of the atmosphere. In a mixture of two liquid constituents, each may be regarded as being dissolved in the other, with the result that each lowers the vapor pressure of the other. In the case of mixtures of Class III, the vapor pressure rises to a maximum at which it remains constant, which means that a constant **minimum** boiling point is reached. When such a mixture is obtained, further separation of the constituents is impossible since the composition of the distillate is identical with the composition of the mixture in the distilling flask. A mixture containing 95.57 per cent by weight of alcohol and 4.43 per cent by weight of water represents a constant boiling mixture of these two substances, which boils at a temperature of 78.15°C., a boiling point slightly below that of pure alcohol, which is 78.3°C. This explains why it is impossible to prepare absolute alcohol by fractional distillation. This can be accomplished only by using chemical dehydrating agents to remove the last traces of water.

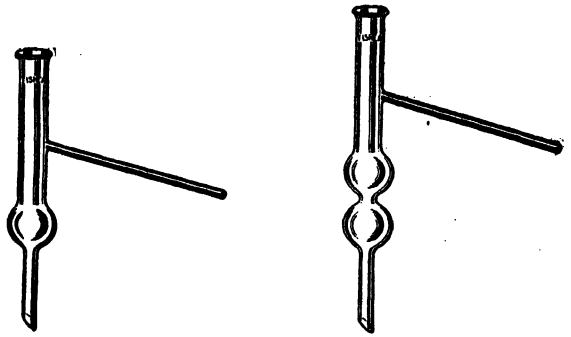
Fractional Distillation of Alcohol.—The separation of alcohol and water is an example of the practical application of fractional distillation that is of considerable industrial and pharmaceutical importance. Since alcohol boils at approximately 78°C. and water at 100°C., it might be assumed that, by heating the mixture and collecting the distillate until the temperature reaches the boiling point of water, all the alcohol could be separated.

However, the distillate will be found to consist of a mixture of alcohol and water; for even though water does not boil at temperatures below 100°, its vapor pressure is fairly high; even at the boiling point of alcohol. If the distillate is subjected to redistillation, being heated again to 100°C., a higher proportion of water will be left in the distilling flask. Theoretically, if redistillation is repeated a sufficient number of times, it is possible to obtain nearly pure alcohol as the distillate, the upper limitation on the percentage of alcohol being that of the constant boiling mixture, containing 95.57 per cent by weight.

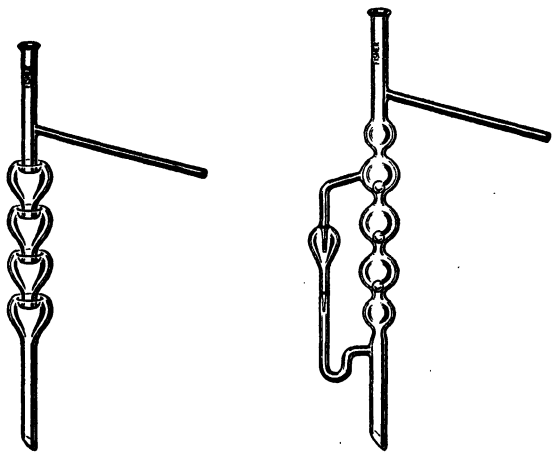
In actual practice, it is found more convenient to collect the product of each distillation in a number of flasks, the receiving flask having changed at predetermined temperature levels as the boiling point of the mixture rises. For example, that portion coming over at a boiling range up to 85°C. might be collected in one flask, another fraction between 85 and 90°, and a third between 90 and 95°. The first fraction collected (below 85°) will contain most of the alcohol, whereas the last fraction (90 to 95°) will contain a much lower proportion. If the intermediate fraction is redistilled separately and fractionation continued at the same temperature intervals, those portions distilling below 85° will ultimately contain most of the alcohol. If these fractions are now mixed with the fraction originally obtained at the same temperature interval and the mixture is again distilled, the fractions being collected this time at smaller temperature intervals, as, for example, 2° each, these operations will eventually yield a liquid having a boiling point approximating that of alcohol and no further separation will be possible.

Fractionating, or Distilling, Columns.—The discussion of the fractional distillation of alcohol that precedes is probably sufficient to indicate that this is a rather complex and tedious process, because of the time consumed in the redistillation of the separate fractions and the number of fractions to be collected. Fortunately, it has been found that much time may be saved by the use of fractionating, or distilling, columns interposed between the boiler and the condenser. Several types are shown in Fig. 87.

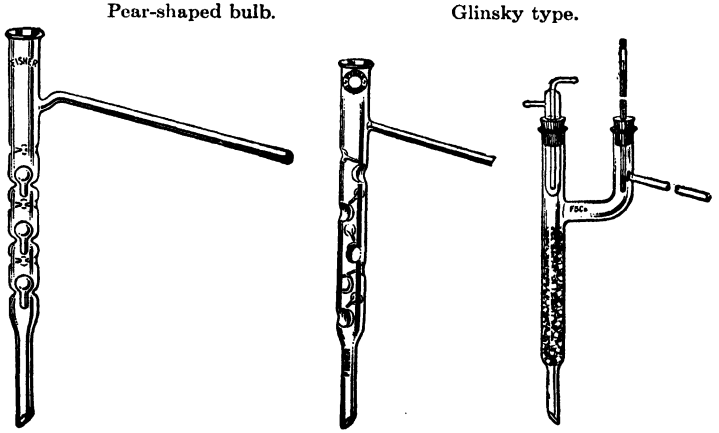
The fractionating column acts by condensing the less volatile constituent of the vapor as it makes its way up the tube.



Bulb forms.



Pear-shaped bulb. Glinsky type.



Snyder floating-ball type. Modified Vigreaux type. Cold-point type.

FIG. 87.—Distilling or fractionating columns.

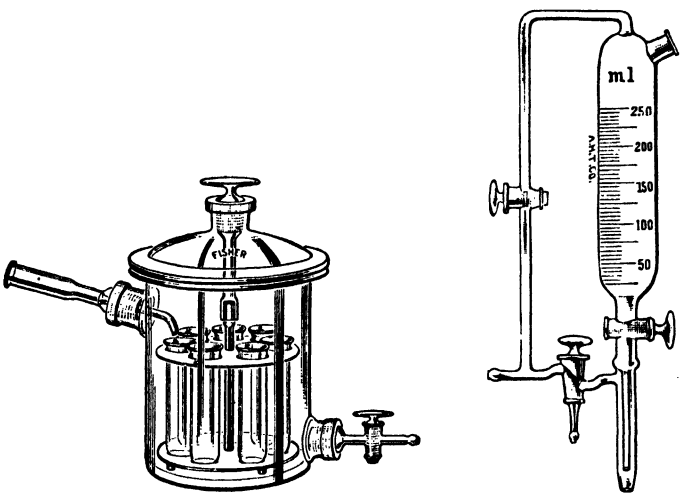
Although the theory of its use is extremely complicated, the effect is that of continual redistillation as the vapors rise through the column. At each step in the column, the concentration of the more volatile liquid tends to increase progressively, with the result that the distillate will show a concentration of the more volatile constituent which compares favorably with or may exceed that obtained as the result of repeated fractionations and redistillations without the use of the fractionation column.

For large-scale operations, full advantage is taken of the principle involved in the use of the **fractionating, or rectifying, column.** This is especially true in the commercial production of alcohol and distilled spirits and in the distillation of petroleum products. Large fractionating columns of this type are frequently made of copper or other metals, the interior being coated with tin. It is usually necessary to provide insulation for the column in order to prevent loss of heat, which otherwise would permit excessive condensation of the more volatile constituent. When a large column is to be designed for a particular purpose, considerable experimentation is required with small-scale models, in order to determine the quantity of heat necessary to produce the desired concentrations at the various levels in the column. From the experimental data obtained, it is possible to design large-scale units suitable for industrial use.

Fractional Distillation under Reduced Pressure.—As was previously mentioned in connection with constant boiling mixtures, such as that produced by hydrochloric acid and water, the belief was formerly held that a definite chemical combination of the acid and the water accounted for the uniform composition of the vapor and the resulting distillate. It was discovered, however, that such constant boiling mixtures could exist only at constant pressure and that a change in pressure would result in a change in proportions of the components in the distillate. This discovery is of considerable importance since distillation under reduced pressure may be used to overcome the formation of constant boiling mixtures.

Another application of fractional distillation under reduced pressure, which is of greater pharmaceutical interest, is in the separation of the constituents of volatile oils by direct distillation. The naturally occurring volatile oils are extremely complex

mixtures, often containing hydrocarbons, terpenes and sesquiterpenes, alcohols, esters, aldehydes, ketones, phenols and phenolic compounds, oxides, lactones, nitrogenous compounds, compounds containing sulfur, and free organic acids. Although several of these constituents may be isolated by chemical means, as in the separation of phenols, for example, by treatment with fixed alkalies, the constituents usually are so numerous and so varied in composition that physical methods must be used to effect the separation of some of them. Most of these constituents possess



Bruehl type. Bogert type.

FIG. 88.—Fractionating receivers.

relatively high boiling points but are altered chemically if heated to a sufficiently high temperature to produce boiling. Fractional distillation under reduced pressure is particularly well adapted to the separation of these constituents. For this purpose, it is necessary to use some type of receiver that will permit the collection of the successive fractions of the distillate without interrupting the process by interfering with the partial vacuum in the closed system. Two such devices are shown in Fig. 88. It will be noted that the Bruehl distillation receiver resembles a vacuum desiccator in some respects and is equipped with a turntable bearing individual tubes for the separate fractions. The turntable may be rotated by turning the handle at the top of the

receiver without having to open the system, which would destroy the partial vacuum.

The Bogert distillation receiver permits the collection of an unlimited number of fractions without interruption of the partial vacuum in the system. The fractions are collected by closing the appropriate stopcocks so that the receiving flask may be changed without interfering with the partial vacuum in the closed distilling system. By proper manipulation of the stopcocks, the pressure in the flask which replaces that used for the collection of a given fraction may be reduced to the same level as that maintained in the rest of the system before any of the distillate is permitted to flow into the receiving flask.

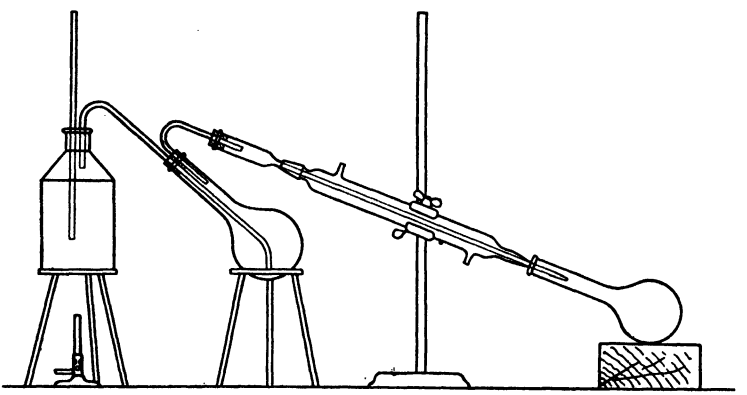


FIG. 89.—Steam distillation.

When fractional distillation under reduced pressure is carried out upon a volatile oil, especially in conjunction with the use of a suitable fractionating column, fairly complete separation of the constituents into fractions of rather narrow boiling-point ranges is usually obtained.

Steam Distillation.—A liquid that is immiscible with water and that has a relatively high boiling point may be distilled at a temperature far below its normal boiling point by the simple expedient of boiling it with water or passing a current of steam through it. This process is of particular importance in the production of the volatile oils, since many of the normal constituents of these oils have such high boiling points that they would be decomposed if an attempt were made to obtain them

by direct distillation from the plant materials containing them. At first thought it appears unreasonable to expect that appreciable quantities of a higher boiling substance could be distilled at a temperature equal to, or below, the boiling point of water. But an understanding of the behavior of immiscible liquids when heated together explains why this is possible.

Theoretical Considerations.—Steam distillation is based upon the fact that immiscible liquids behave quite differently from miscible liquids when subjected to heat. As was pointed out in the discussion of fractional distillation, in the case of liquids that are mutually soluble in each other in all proportions, or miscible, the presence of each component has the effect of reducing the vapor pressure of the other. But in the case of immiscible liquids, neither of the liquids has any perceptible effect upon the vapor pressure of the other. In a mixture of two immiscible liquids, boiling occurs whenever the sum of the individual vapor pressures is equal to 760 mm. of mercury. Hence, if the non-aqueous component shows an appreciable vapor pressure at the boiling point of the mixture, this temperature must be below the boiling point of water.

Many volatile oils, such as oil of peppermint, oil of cinnamon, oil of clove, and oil of turpentine, are obtained by steam distillation. The boiling point of oil of turpentine may vary within certain limits, but it is usually about 160°C. When it is mixed with water, however, the boiling point of the mixture is approximately 95.6°C. Reference to the table of the vapor pressure of water at various temperatures[1] shows that the vapor pressure of water at this temperature is approximately 648 mm. of mercury. Since the mixture of liquids boils at this temperature, it follows that the total of the two pressures must be 760 mm.; hence the vapor pressure of the oil of turpentine must be 760 − 648, or 112 mm. of mercury.

If, instead of oil of turpentine, which is not a pure compound but a mixture of substances, a pure chemical is considered with relation to its behavior with steam, it is possible to calculate the approximate proportions of the substance and of water that will be found in the distillate. Nitrobenzene ($C_6H_5NO_2$) is such a liquid, having a molecular weight of approximately

[1] N. A. LANGE. "Handbook of Chemistry," 2d ed., 1937, Handbook Publishers, Inc., Sandusky, Ohio, p. 1203.

123 and a boiling point of approximately 211°C. It is very slightly soluble in water; but, for all practical purposes, we may consider it as an example of an immiscible liquid. A mixture of nitrobenzene and water boils at 99°C. Reference to the table of the vapor pressure of water at various temperatures already cited shows that at this temperature water has a vapor pressure of 733 mm. of mercury. Accordingly, the pressure of nitrobenzene must be 760 − 733, or 27 mm. of mercury.

According to Avogadro's hypothesis, equal volumes of gases, under the same conditions of temperature and pressure, contain equal numbers of molecules. Hence, the weights of equal volumes of different gases, under the same physical conditions, must be proportional to the molecular weights of the compounds. The molecular weight, in grams, of any gas at 0°C. and 760 mm. of pressure occupies 22.32 L. Correcting for the temperature of 99°C. (the boiling point of the water and nitrobenzene mixture), the molecular weight of any gas, in grams, would occupy, according to Charles's law,

$$\frac{23.32(273 + 99)}{273} = 30.41 \text{ L.}$$

However, the volume of each component in the mixture of vapors would be approximately in proportion to their vapor pressures, *i.e.*, 27 volumes of nitrobenzene to 733 volumes of water vapor. Hence, in 30.41 L. of the mixed vapors at 99°C. there would be

$$\frac{27 \times 30.41}{760} = 1.08 \text{ L. of nitrobenzene vapor}$$

and

$$\frac{733 \times 30.41}{760} = 29.33 \text{ L. of water vapor}$$

On the basis of volume, it is apparent that approximately twenty-seven parts by volume of water vapor are distilled for each volume of nitrobenzene vapor. (29.33 ÷ 1.08 = 27.157.) In order to compute the weights of the two products that are obtained, the molecular weights of the two compounds must be considered. The calculation of the weights of each component contained in 30.41 L. of the mixed vapors at 99°C. would be made as follows:

$$\frac{1.08 \times 123}{30.41} = 4.37 \text{ Gm. of nitrobenzene}$$

and

$$\frac{29.33 \times 18}{30.41} = 17.36 \text{ Gm. of water}$$

That is, one part of nitrobenzene (by weight) is yielded for approximately each four parts by weight of water. (17.36 ÷ 4.37 = 3.97.) Thus it is seen that a volume ratio of 1 to 27 corresponds to a weight ratio of 1 to 4. The difference in the molecular weights of the two compounds is, of course, the factor that offsets the apparent disadvantage of the relatively low vapor

pressure of the nitrobenzene. An understanding of the reasoning involved in the explanation just given is of value in judging whether or not steam distillation may be used profitably for other immiscible liquids. Experience has shown that the process may be used to advantage, even with immiscible liquids having considerably lower vapor pressures at the boiling point of the mixture than that shown by nitrobenzene, provided that the molecular weight of the compound is sufficiently larger than that of water to compensate for this factor. If the boiling point of the mixture is known or determined, it is possible to calculate in advance the approximate composition of the distillate that will be obtained.

Florentine Receivers.—In the application of steam distillation to the production of volatile oils, some method must be employed to separate the volatile oils from the water that is distilled with them. Since, in most cases, the quantity of water is relatively large as compared with the yield of volatile oil, it is advantageous to have the separation carried out automatically as a continuous process. This is usually accomplished by the use of special traps known as **Florentine receivers.** Two kinds of receiver are used, one designed for the collection of liquids lighter than water and the other for liquids heavier than water. Or, if desired, a combined form, suitable for the collection of both types of liquid, may be used by closing off the appropriate overflow tube.

Most of the volatile oils official in the Pharmacopoeia and the National Formulary are lighter than water, and the receiver for liquids of this type is accordingly most frequently used. Only the oils of bitter almond, clove, cinnamon, and sassafras, of the Pharmacopoeia, and oil of pimenta, of the National Formulary, are heavier than water.

As can be seen in Fig. 90, the Florentine receiver for liquids lighter than water consists of a container provided with a bent overflow tube, which has its lower opening on the side of the container near its bottom. The overflow tube extends upward for some distance and is then bent downward at a point below the upper rim of the receiver. The position of the upper bend in the overflow tube determines the level of the liquid that will be maintained in the receiver.

At the beginning of the process of distillation, a sufficient quantity of water is placed in the receiver to cover the opening of the overflow tube. As the distillate is collected, the volatile oil that separates from the water rises to the surface, because of its lower

specific gravity, while the water forms the lower layer. As the level of the liquid reaches that of the upper bend in the overflow tube, the water is discharged from the receiver while the oil is retained. The water that is collected is, of course, saturated with the volatile oil. It may be marketed in this form as an aromatic water, or it may be redistilled fractionally in order to recover a portion of the oil that is held in solution. In such cases, the reprocessing of the water is spoken of as **cohobation.**

The receiver for collecting liquids heavier than water has a short overflow tube located near the top of the receiver. This permits the discharge of the lighter supernatant layer, which is

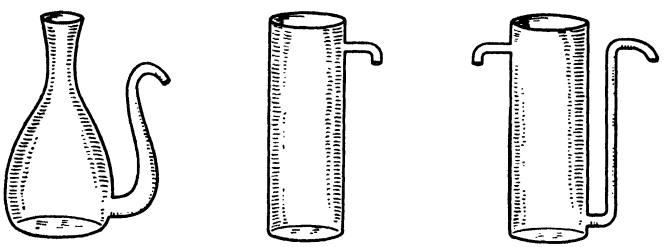


FIG. 90.—Florentine receivers.

the water, while the heavier oil separates as the lower layer in the receiver.

Destructive Distillation.—The process of **destructive distillation,** also known as **dry distillation,** consists in applying strong heat to organic matter that is protected from air and condensing the volatile decomposition products that are formed. The chemical changes are reactions involving partial decomposition, since the products that are obtained are always less complex than the original substances being distilled. For the most part, destructive distillation is limited in its application to two naturally occurring substances—wood and coal. The destructive distillation of both these is essentially a large-scale industrial process, and for this reason no detailed study will be made of it. However, the products obtained from coal and wood are so important that brief mention will be made of them. Since high temperatures are involved and the operations yield a solid residue (charcoal from wood and coke from coal), the stills that are used

consist of large open vessels of cast iron, having a flange at the top and a dome with a corresponding flange provided with a tube for carrying off the volatile products. The connection between the still and dome is made airtight by being luted with fire clay, and the dome is usually held in place by means of iron clamps.

Brief mention was made of the process of destructive distillation in connection with Carbonization in Chap. X. It was pointed out there that wood yields such products as acetone, methyl alcohol, acetic acid, creosote, and tar.

Coal-tar Products.—The development of coal-tar products and the chemistry of the aromatic hydrocarbons dates from 1856, when the English chemist W. H. Perkin, in an unsuccessful attempt to synthesize quinine, accidentally discovered a coal-tar dye while experimenting with a coal-tar derivative. The value of coal tar at once became recognized, and today it represents a most important source, not only of dyestuffs, but of medicinal substances, solvents, flavors, perfumes, photographic chemicals, and explosives.

The coal-tar industry may be regarded as a by-product of the steel industry, since coke is essential for the reduction of iron ores. When bituminous coal is heated in the coke oven, the products consist of the residue, coke, and the volatile substances, which are illuminating gas, ammonia, and coal tar. Coal tar is a highly complex mixture of compounds that is separated into its many valuable constituents by distillation at gradually increasing temperatures. The operation is usually carried out in a cylindrical iron still having a concave bottom and a domed top. The charge usually consists of 20 tons of coal tar, which has previously been freed from its moisture content. The distillate is passed through a condensing coil surrounded by water, which is cold at first but which is alternately changed from cold to hot throughout the process as required, in order to prevent clogging of the coil by the solid substances that would otherwise separate out.

This preliminary distillation yields the following four fractions: (1) light oils (sp. gr. 0.90 to 0.95), which are collected up to a temperature of 172°C. and represent 2 to 8 per cent of the coal tar; (2) middle, or carbolic, oils (sp. gr. 1.01), collected between 172 and 230°C. and corresponding to 8 to 10 per cent of the coal tar; (3) heavy, or creosote, oils (sp. gr. 1.04), distilling between 230 and 270°C.; (4) anthracene oils (sp. gr. 1.10), collected between 270 and 400°C. in an amount corresponding to 16 to 20 per cent of the original charge of tar. The residue, known as coal-tar pitch, represents approximately 50 per cent of the original weight. This material is used as a roofing material and also serves as an artificial asphalt, used in paving.

These preliminary fractions are treated in various ways in order to isolate their many ingredients. The light oils are first redistilled to separate them from a small proportion of the middle, or carbolic, oils. Then the purified

fraction is treated with concentrated sulfuric acid. This operation fixes the bases and dissolves or resinifies the unsaturated hydrocarbons, the phenols, and the sulfur compounds. The acid portion is separated and yields ammonium sulfate and pyridine. The oil is then washed with water and a weak solution of sodium hydroxide and, after drying, is subjected to fractional distillation.

The four following fractions are collected: (1) the "first runnings," the portion collected up to a temperature of 70°C., consisting chiefly of carbon disulfide, hexane, and aceto-nitrite; (2) light benzol, collected between 70 and 122°C.; (3) heavy benzol, collected between 122 and 177°C.; (4) carbolic oils, which are returned for further processing to the preliminary fraction of carbolic oils.

The crude benzol that is thus obtained is distilled again and separated into pure benzol (benzene), toluene, xylene, and a residue known as *solvent naphtha*. The latter is used extensively in the rubber industry as a solvent for rubber. The benzol is used in the manufacture of motor fuel and illuminating gas and as a "dry cleaner" in laundry work.

The middle, or carbolic, oils contain naphthalene, phenol, and cresols. The naphthalene crystallizes out and is separated by centrifuging. The phenolic bodies, which may represent as much as 30 to 40 per cent of this fraction, are separated by treatment with 10 per cent sodium hydroxide solution, which forms soluble phenates. The phenols are recovered by acidulating the aqueous solution. They are again distilled fractionally and then chilled; this causes the phenol to crystallize and leaves the cresols, which are present as a liquid. The phenol may be used in that form or as a source for picric acid (trinitrophenol), salicylic acid, and other derivatives. The cresols (a mixture of the three isomeric forms, *ortho*, *meta*, and *para*) are usually not separated but are employed in this crude form as a disinfectant.

The heavy, or creosote, oils usually contain neutral and acid oils consisting principally of naphthalene, dinaphthalene, xylenol, naphthol, and paraffins. The creosote oils are used chiefly for preserving timber and as disinfectants.

The anthracene oils contain some phenol in addition to the anthracene, the latter being crystallized by chilling the oils to a point at which the anthracene separates in a solid form, known as *crude anthracene*. This solid material is then subjected to a pressure of 3,000 to 4,000 lb. per sq. in. in a hydraulic press and heated with steam. Nearly all the naphthalene and phenanthrene present flow out in liquid form. The residue of anthracene is washed with solvent naphtha and with the acid pyridine obtained from the first treatment of the oils, resulting in anthracene of 90 per cent purity.

Upon oxidation, anthracene yields anthraquinone, from which in turn alizarin is derived. The fluid remaining after treatment of the light oils with sulfuric acid contains pyridine and other bases, as the picolines and lutidines. Ammonia is run into the liquid until the pyridine separates. Quinoline is separated in the same manner from the sulfuric acid washings of the heavy oils. These secondary products yield an extensive list of medicinal chemicals, perfumes, flavors, disinfectants, preservatives, fuel and lubricating oils, pigments, photographic chemicals, and explosives.

Space does not permit a complete listing of the derivatives of coal-tar products of pharmaceutical interest. Among the more important of the primary substances isolated from coal tar that yield important medicinal substances are the aromatic hydrocarbons, benzene, toluene, naphthalene, and anthracene, and two substitution products of benzene, namely, phenol and cresol. Benzene serves as a starting point for the synthesis of such compounds as nitrobenzene, aniline, acetanilid, acetophenetidin, pyrocatechol, resorcinol, hydroquinone, quinone, pyrogallol, and phloroglucinol. Phenol yields salicylic acid, phenyl salicylate, methyl salicylate, coumarin, trinitrophenol, and a series of amidophenol dyes. Toluene may be used as a source for benzaldehyde, benzoic acid, mandelic acid, saccharin, and the high explosive, trinitrotoluene. Naphthalene yields α-naphthol, β-naphthol, phenolphthalein, and a series of amidonaphthol dyes. Anthracene yields anthraquinone, which in turn serves as a source for a very important series of dyestuffs known as the alizarin dyes.

Sublimation.—The process of **sublimation** may be defined as the heating of a solid that vaporizes directly from the solid phase without fusion and recovering the solid by condensing the vapor. The transformation of the vapor to the solid state is also made directly without liquefaction. The object of the process is the purification of volatile solids by separating the latter from nonvolatile impurities that may be present. The process is limited in its application by the fact that this abnormal behavior is exhibited only by a relatively small number of compounds, under ordinary conditions of pressure.

The question of why some substances sublime while others do not is answered by an examination of their physical properties. When a solid that is incapable of sublimation is heated, fusion occurs. If the heat is continued, the resulting liquid boils at a point at which its vapor pressure is equal to the external pressure. But when a substance such as iodine, for example, is heated, it is observed not to melt, but to pass directly into the gaseous state, forming the characteristic purple vapors of iodine. When these vapors are cooled, solid crystals of iodine are formed directly from the vapor. This difference in behavior may be explained by the fact that any substance which **sublimes** upon heating

has a vapor pressure, at its melting point, which is equal to the atmospheric pressure, while a substance which melts upon heating has a vapor pressure, at the melting point, which is less than that of atmospheric pressure and consequently requires further heating to increase its vapor pressure to that of the atmosphere before it boils.

When the external pressure is increased, the boiling point is raised. If the pressure is reduced, the boiling point is lowered. On the other hand, it has been found that the melting point of a solid is only slightly affected by changes in the external pressure. This effect of changing pressure upon melting points is so slight that ordinarily it is ignored, whereas an observation of the atmospheric pressure is considered necessary for calculation of the true boiling points of liquids. Theoretically, it should be possible to heat, under increased pressure, a substance which sublimes at normal pressure and thereby raise its boiling point to a temperature at which the substance would undergo fusion before changing to the gaseous state, without changing its melting point to any appreciable extent. Experiments which have been carried out upon substances capable of sublimation under normal pressure, such as arsenic trioxide, have shown that this occurs. Not only is this true, but it is also possible, by reducing the pressure, to lower the boiling point of a substance that does not normally sublime to the same temperature as its melting point, with the result that the solid vaporizes under these special conditions. If the reduced pressure is maintained on the vapor, it will, upon cooling, pass directly into the solid state. Although a considerable number of compounds are known that have sufficiently high vapor pressures to make sublimation possible, only a few are commonly purified by this method. Those of especial interest in pharmacy are the following: ammonium carbonate, ammonium chloride, arsenic trioxide, benzoic acid, camphor, iodine, mercuric bichloride, mild mercurous chloride, sulfur.

The process of sublimation when used as a manufacturing process is usually carried out as a large-scale operation, as in the production of ammonium chloride or sublimed sulfur. It is also used to some extent as a means of purification in analytical chemistry. The process may easily be demonstrated on a small scale by applying slow heat to benzoic acid contained in a dish

over which a glass funnel has been inverted. A towel moistened with water may be wrapped around the funnel for the purpose of cooling. If a funnel is selected that is of slightly greater diameter than the dish, a stream of cold water may be made to flow over the outer surface of the funnel for the same purpose. Care must be exercised to prevent the water from running into the dish. At one time the process of sublimation was officially prescribed for benzoic acid. The procedure recommended was to place the benzoic acid in a shallow tinned iron pan, the top of which was covered by pasting a sheet of bibulous paper (filter paper) over the edge of the dish. The vapors of the acid were forced to pass through the pores of the paper as a further precaution in purifying the product. Condensation was effected by placing a large cone of stiff paper or pasteboard over the dish. The cooling effect of the surrounding air was usually sufficient to bring about condensation.

Cake Sublimates.—The temperature at which the vapors of a substance are solidified has an important bearing on the physical form of the sublimate. Three kinds of sublimates are known—**cake sublimates,** as represented by camphor and mercuric bichloride, **powder sublimates,** such as mild mercurous chloride or sulfur, and **crystal sublimates,** as typified by iodine and benzoic acid. Because of the low temperatures at which the vapors condense, the form of apparatus differs considerably from that used in distillation. The receiver serves both as receiver and condenser; and since the condensed substance is a solid, it cannot be made to flow away from the point at which it solidifies. It follows that the neck of the heating vessel must be wide in diameter, to prevent clogging by the sublimate, and as short as possible in order to avoid excessive distances for the vapors to travel.

The conditions of temperature in the receiver determine in many cases the nature of the sublimate obtained. If the temperature is relatively high, approximating that of the vapor, it is possible to prevent the formation of the sublimate until the vapors strike the cooler surface of the condensing chamber. Under these conditions, the sublimate is deposited layer by layer upon this surface, from which it may be removed in solid masses or cakes, by scraping with a spatula.

Powder Sublimates.—If, on the other hand, the air in the condensing chamber is considerably cooler than the entering vapors, a condition that may be brought about by providing adequate ventilation of the condenser, the vapors may be made to condense in mid-air, so to speak, almost upon contact with the cooler atmosphere. This produces a finely powdered sublimate which falls to the bottom of the receptacle in that form.

Crystal Sublimates.—Some substances sublime in distinct crystalline forms if the conditions are properly controlled. As a general rule, camphor tends to form a cake sublimate; but if the temperature is adjusted so that the condensation takes place very slowly, the sublimate is crystalline. There are other substances, such as benzoic acid, iodine, menthol, and naphthalene, that normally solidify in distinct crystalline forms in any style of condenser. In this connection, it is of some historical interest to note that sublimates having a crystalline structure were formerly designated by the term **flowers** and that benzoic acid, for example, was known as **flowers of benzoin,** or **flowers of benjamin,** having first been obtained by heating the balsam of benzoin (also known as gum benjamin). Similarly, sublimed sulfur is known as **flowers of sulfur.** It is supposed that the more or less symmetrical arrangement of the crystals as they condensed in the form of tufted needles suggested a similarity to the arrangement of the petals of a flower.

STUDY QUESTIONS

1. What two processes are involved in distillation?

2. What is the difference between an alembic and a retort type of still?

3. Explain the phenomenon of bumping of a boiling liquid, and explain the procedures that may be used to overcome this difficulty.

4. What is entrainment, and what devices are used to prevent its occurrence?

5. What relation exists between the heat of vaporization of a liquid and the ease or difficulty with which its vapors may be condensed?

6. What is an air condenser?

7. What characteristics of design and construction of a condenser contribute to its efficiency?

8. What is the special purpose for which reflux condensers are used?

9. What are the advantages and disadvantages of the worm condenser?

10. Explain the principle of operation of the Soxhlet extractor.

11. Describe the procedure recommended by the National Formulary for the preparation of redistilled water.

12. What is the effect of reducing the pressure on the boiling point of a liquid?

13. What classes of pharmaceutical preparations require distillation at reduced pressure in their manufacture?

14. Explain the principle of operation of the water pump or aspirator used in reducing the pressure for distillations under reduced pressure.

15. What is the theoretical limitation on the reduction in pressure that can be attained by the use of the water pump?

16. What is a manometer, and for what purpose is it used?

17. Why is a glass flask unsuited for the preparation of solid extracts of drugs by distillation under reduced pressure?

18. What is the usual object of the process of fractional distillation?

19. List the types of mixtures of liquids that are commonly subjected to fractional distillation.

20. The behavior of miscible liquids upon fractional distillation may fall into any one of three patterns. Describe fully the characteristics of behavior of each type of mixture.

21. What limitation on the separation of miscible liquids that produce constant boiling mixtures is observed in fractional distillation?

22. In what way may a still further separation be attained even if a constant boiling mixture of miscible liquids has been produced?

23. What is the advantage of the use of the fractionating column in fractional distillation?

24. What special applications are made of fractional distillation under reduced pressure?

25. Explain the theory of steam distillation.

26. A hypothetical immiscible liquid A is assumed to have a boiling point of 190°C. and a molecular weight of 150. When subjected to steam distillation, the mixture has a boiling point of 95°C. The vapor pressure of water at 95°C. is 633.9 mm. of mercury. Calculate the proportion of compound A, both by volume and by weight, that will be obtained in the vapors coming from the distilling flask.

27. Define the process of destructive distillation.

28. What are the principal applications of destructive distillation?

29. List some of the more important chemicals of pharmaceutical interest derived from coal tar.

30. Explain why some solids may be sublimed upon heating, while others undergo fusion and ebullition before being vaporized.

31. Explain how a solid that does not sublime ordinarily may be made to do so under special conditions.

32. Under what special conditions may a solid that normally sublimes be prevented from doing so and be forced to undergo fusion?

33. Name those products of pharmaceutical interest which are usually purified by sublimation.

34. Three kinds of sublimates are known. Name them, and explain how each is formed.

35. Why are some sublimates spoken of as flowers?

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CHAPTER XII

SOLUTIONS

It is obvious that solutions of one kind or another play an important part in pharmacy. One author has said that many of the remarkable phenomena of nature are directly concerned with solutions. This is particularly true in respect to biologic phenomena, in which, to a significant degree, solutions of pharmaceutical substances play the important role of assistants to nature. The pharmacist must therefore know much about solutions.

The word *solution* is applied to a mixture of two or more substances which is so intimate that it has become physically homogeneous. The mixture may consist of molecules, atoms, ions, or a combination of all three. The distribution of each component throughout the other is on a molecular, atomic, or ionic basis rather than on the basis of particles of larger size. The percentage composition of solutions can be varied within wide limits without destroying their homogeneity. Compounds are also homogeneous, but since they are not mixtures their percentage composition is fixed. This fact gives us a good basis for the definition of a solution that is commonly known to be a homogeneous mixture whose composition can be varied between wide limits.

When speaking of solutions we say that one substance is dissolved in another. The dissolved substance is known as the **solute,** and the substance in which the solute is dispersed is known as the **solvent.** Usually that which is present in the larger quantity is designated as the solvent, but the choice is purely arbitrary. Custom has decreed that when water is one of the ingredients in a solution it is usually considered the solvent. This explains why the pharmacopoeial mixture of 95 per cent alcohol and 5 per cent water is called a 95 per cent solution of alcohol in water. Another anomaly is the official liquefied phenol, which contains about 88 per cent phenol and

12 per cent water. It is ordinarily thought of as a solution of phenol in water. As a matter of chemical fact, the reverse is true.

Types of Solution.—One normally thinks of solutions as being formed by placing a solute in a liquid solvent, because this is the most common type. Actually, substances in any of the three states of matter can function as solvents as well as solutes. Gases, liquids, or solids can function either as solute or solvent. It is possible, therefore, to have nine types of solution, all of which, however, are not of equal importance in pharmacy.

Solutions of Gases in Liquids.—Solutions of this kind have frequent application in pharmacy. Dissolved gases such as carbon dioxide, ammonia, and hydrogen chloride find constant use in the manufacturing, compounding, and administering of medicines. The use of carbon dioxide in solutions of nauseous or irritating medicines to make them palatable has become one of our important medical techniques. Its effectiveness as a disguiser of taste presumably lies in the ability of the gas as it escapes from solution to collect as tiny bubbles over the surface of the taste buds. A protective coating is thus formed, which keeps the disagreeable solution away from the organs of taste. Generally speaking, the carbon dioxide is not introduced as such from an outside storage container. Instead it is generated in the mixture by means of a chemical reaction. This is usually brought about by a reaction between a bicarbonate and/or carbonate and an acid. The reaction involving sodium bicarbonate and citric acid is typical.

$$3NaHCO_3 + H_3 \cdot C_6H_5O_7 \rightarrow Na_3C_6H_5O_7 + 3CO_2\uparrow + 3H_2O$$

Tartaric acid ($H_2 \cdot C_4H_4O_6$) is also used in combination with citric acid to furnish the hydrogen ions required for the reaction.

The manufacture and use of the official effervescent salts and of effervescent tablets are based on the value of carbon dioxide dissolved in water as a palatable vehicle.

When the pharmacist is called upon to dissolve a gas in a liquid, he should realize that if the gas is only moderately soluble the application of pressure, provided that the temperature remains constant, will facilitate solution. This is in accordance with Henry's law, which states that "the weight of a gas that

dissolves in a given liquid is directly proportional to the pressure, provided the temperature remains constant." He should also bear in mind that gases are less soluble in warm than in cold solvents.

A disturbing factor which might result in incompatibilities, in prescriptions or other manufacturing difficulties is the fact that frequently solutions of this kind acquire properties not possessed by either the gas or its solvent. The acquisition of acidic or basic properties is most common. Chlorine gas dissolved in water illustrates this. Some of the chlorine reacts with the solvent to form two acids.

$$Cl_2 + H_2O \rightarrow HCl + HClO$$

Ammonia dissolved in water immediately forms some basic ammonium hydroxide.

$$NH_3 + H_2O \leftrightharpoons NH_4OH$$

Solutions of Liquids in Liquids.—Many prescriptions are solutions of liquids in liquids. As the pharmacist works, he discovers that the liquids he uses act toward each other in one of two ways. Either they mix freely in all proportions, or each is only partly soluble with respect to the other, this partial solubility at times being so slight as to be considered negligible. In the former situation the fluids are said to be **miscible** with each other. Fluids that do not mix with each other are said to be **immiscible.** Alcohol and water are examples of miscibility and chloroform and water of immiscibility. Water and ether represent the condition in which two fluids are partly miscible because each is partly soluble in the other.

Two important properties of the liquids being mixed are changed as a result of solution. In mixing, each liquid diminishes the vapor pressure of the other so that the vapor pressure or volatility of the solution is never so great as the sum of the original vapor pressures. It may be greater or less than that of either fluid, its value depending on the relative concentration of components. The vapor from the solution at a given temperature will be a mixture formed by the liquids having appreciable vapor pressures. Vapor pressures might be considered to

advantage when prescriptions for inhalation are being formulated. The boiling point of a solution may also be higher or lower than that of either of its constituents. Usually it is an intermediate value. The situation is further complicated by the fact that in general the ratio of the vapors escaping from the solution is not the same as the ratios of the liquids they are leaving. This means that the composition of the solution is changing constantly during boiling, resulting in a steady change in boiling point and variation in the composition of the vapors. Inhalation prescriptions therefore do not furnish constancy of medication.

Solution of Solids in Liquids.—Solids dissolved in liquids constitute the majority of our true solutions. It is well to remember in this connection that some solids appear to dissolve in a liquid when in point of fact they are insoluble. The apparent solubility is due to a chemical reaction that takes place between the added substance and the liquid to form a soluble compound that goes into solution the instant it is formed. Zinc is said to dissolve in hydrochloric acid. Actually, the acid converts the insoluble metal into soluble zinc chloride ($ZnCl_2$). The solution therefore contains zinc chloride instead of zinc.

When making solutions of solids in liquids the pharmacist is often asked to saturate the solvent with the solute. Prescriptions for boric acid, sodium borate, and potassium iodide ordinarily call for saturated solutions. The manufacturing pharmacist frequently prepares saturated solutions by adding to the solvent an excess of solute and heating the mixture, with stirring. When the solvent has taken up all the solute it possibly can for the higher temperature, it is allowed to cool. At room (constant) temperature an equilibrium is established between the dissolved solute and its undissolved particles collected at the bottom of the container.

$$\text{Solid solute} \rightleftharpoons \text{dissolved solute}$$

In this dynamic equilibrium there is a constant return of dissolved material to its original solid form, which is exactly balanced by solute molecules going into solution; for a **saturated solution** results from the establishment of such an equilibrium between the solute and solvent, and is defined as **one that is in equilibrium with the undissolved solute.**

It is well to remember that each temperature has its own equilibrium and that the quantity of solute required to saturate the solvent varies with temperature. Generally speaking, as the temperature increases the solvent will require more solute to saturate it. A solution saturated at higher temperatures loses its excess solute by crystallization as it cools, **provided that some of the solid is present at all times** to act as a focus for crystal formation. If no solid is present during the cooling of a saturated solution, it occasionally happens that the excess solute fails to crystallize out. In such circumstances, the solution becomes **supersaturated,** *i.e.*, it contains more than the saturation quantity of solute for the lower temperatures. The introduction of the smallest quantity of solid will start crystallization. Sometimes only scratching the inner surface of the container, slight agitation, or even the presence of dust particles is sufficient.

Solubility.—The amount of solute required to saturate a solvent at any given **temperature** and **pressure** is constant. Solubilities, therefore, can be determined with great accuracy. The determinations are easily accomplished by preparing saturated solutions of the solute in the appropriate solvent and analyzing a given quantity of the solution for the amount of solute dissolved. They are ordinarily expressed as the number

TABLE XXI.—U.S. PHARMOCOPOEIA TERMS FOR RELATIVE SOLUBILITIES

Descriptive Terms	Parts of Solvent for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	1–10
Soluble	10–30
Sparingly soluble	30–100
Slightly soluble	100–1,000
Very slightly soluble	1,000–10,000
Practically insoluble	More than 10,000

of grams of the substance required to saturate 100 cc. of solvent at a given temperature. Solubilities in the Pharmacopoeia are expressed on the basis of the number of cubic centimeters of solvent required to dissolve 1 Gm. of solute at a stated temperature. The solubility of Barbital Sodium is given as follows: "One Gm. of Barbital Sodium dissolves in about 5 cc. of water at 25°C." When speaking of the solubility of volatile oils in alcohol of specific strengths the Pharmacopoeia uses still

another method of expression. In the case of Oil of Fennel the Pharmacopoeia states: "Oil of Fennel is soluble in 8 volumes of 80 per cent alcohol and one volume of 90 per cent alcohol." When exact solubilities are not known, it is common to use relative terms in speaking of this property. The Pharmacopoeia has a table of terms covering relative solubilities (Table XXI).

Factors Affecting the Solubility of Solids in Liquids.—It has already been pointed out that **changes in temperature** change solubilities and that usually solids are more soluble in hot than in cold solvents. A few solids such as salt are not particularly affected, being almost as soluble in cold as in hot solvents. There are also certain compounds, notably some of the calcium preparations, that are more soluble in cold than in hot liquids. The official solution of calcium hydroxide must be kept in a cool rather than a warm place, for this reason, in order to maintain its proper concentration. The **state of subdivision** of the solute is important, for a finely divided solute goes into solution faster than one in large particles. **Stirring** or **agitation** also facilitates solution. The **application of heat** is an effective aid to solution, as has already been pointed out. Occasionally time can be saved by making a thick paste of the substance to be dissolved, with only a small quantity of solvent. This procedure thoroughly wets the surface of each solute particle, removing adsorbed air, and facilitates contact with the bulk of the dissolving liquid later on. **Circulatory displacement** such as is recommended by the Pharmacopoeia XII for preparing Mucilage of Acacia is particularly helpful with gummy substances that tend to "ball up" when agitated with the solvent. Actually, the mucilage is made by a modified circulatory technique. In true circulatory displacement the solute is placed in a loosely woven bag near the surface of the solvent. As the solvent dissolves the solute, a solution of greater density than that of the solvent is formed. This settles to the bottom, which makes room for fresh solvent to come in contact with the undissolved solute. A circulation is set up that continues until solution is effected and a liquid of uniform density has been produced. No mechanical agitation is necessary.

Sometimes the solubility of a relatively insoluble substance is greatly increased by the presence of a third substance. For

example, iodine is insoluble in water; but when it is mixed with potassium iodide, a solution is effected immediately. Insoluble mercuric iodide is made readily soluble by the presence of arsenous iodide. Advantage is taken of this aid in preparing the Solution of Arsenic and Mercuric Iodides N.F. VII. Chemicals that thus aid in dissolving otherwise insoluble substances are called **compound solvents.** In the majority of cases they function by forming loose chemical combinations with their associated solutes. The product is soluble. Iodine reacts with the potassium iodide to form soluble I_2KI.

$$I_2 + KI \rightarrow I_2KI$$

In the case of mercuric iodide the situation is apparently not so simple. What probably happens is shown by the following equations:

$$2AsI_3 + 6H_2O \rightarrow 2As(OH)_3 + 6HI$$
$$3HgI_2 + 6HI \rightarrow 3H_2HgI_4$$

Solubilities are affected by the presence of substances already dissolved in the solvent. A solvent partly or completed saturated with a solute will still be able to dissolve other chemicals, but only in reduced quantities. Occasionally it happens that continued addition of the last substance eventually forces the first out of solution. This is called **salting out.** There are procedures in pharmaceutical manufacturing where salting out is an important step. The opposite phenomenon of **salting in** is also sometimes important.

There is no general rule by which we can predict solubilities. It has been stated that substances with similarities in formulas are more likely to be soluble in each other, but the exceptions to this rule outnumber the instances of it.

Concentration of Solutions.—The pharmacist is frequently told to use a dilute solution of one substance and a concentrated solution of another. In the case of the official preparations the strengths are fixed; in almost all other instances the choice of concentration is arbitrary. There is general agreement, however, that solutions containing only a relatively small amount of solute are **dilute** whereas those containing a relatively large amount are **concentrated.** In the Pharmacopoeia most diluted

acids are 10 per cent in strength, while diluted alcohol is nearly 50 per cent ethanol. In clinical work the pharmacist must use solutions whose strengths are expressed in chemical units of weight. Molar solutions are typical. Their concentrations are given on the basis of the number of gram-molecular weights of solute a given volume of solution contains. Accordingly, a **molar solution** (gram-molecular) is one in which one gram-molecular weight of solute is dissolved in a liter of solution. Solutions containing multiples or submultiples of one gram-molecular weight are spoken of as 2 molar, 0.5 molar, and so on.

Normal solutions are likewise important in the clinical laboratory. Here concentration is expressed on the basis of the number of gram-equivalent weights of solute contained in a stated quantity of solution. A normal solution is one in which one gram-equivalent weight of the solute is dissolved in 1 L. of solution. Solutions of other normalities are said to be 2 normal, 0.1 normal, and so on, depending on their gram-equivalent strengths. The gram-equivalent weight of an element is that which is equivalent to 1.008 Gm. of hydrogen or 8 Gm. of oxygen.

Effects Produced by Solution. *Heat of Solution.*—In making a number of pharmaceutical solutions, notably saturated solution of potassium iodide, the pharmacist is struck by the fact that the process results in an unusual cooling effect. Occasionally, with certain other substances, the opposite effect is apparent. These phenomena result from the fact that, when any crystalline solid dissolves, the temperature of the solvent always changes. Generally it falls, because most solids are more soluble in hot than in cold solvents. Heat is absorbed when they go into solution. Solids more soluble in cold than in hot solvents cause the evolution of heat as they dissolve. Heat so absorbed or evolved is called **heat of solution.** It is quantitatively defined as the heat taken up or evolved when 1 Gm. equivalent of solute is dissolved in sufficient solvent to make an infinitely dilute solution. **Heat of dilution** is that heat absorbed when a concentrated solution is diluted.

It is possible for heat of solution to be masked by the heat of reaction evolved when the solute forms a stable compound with the solvent. One of the common illustrations is the heat formed when anhydrous $CaCl_2$ takes up water to become $CaCl_2 \cdot 6H_2O$.

Lowering of the Freezing Point of the Solvent.—Solutes, particularly solids, depress the freezing point of their solvent. In the case of nonelectrolytes there is sufficient regularity in the depression so that molecular weights can be determined by it. We know that if **the gram-molecular weight of any nonelectrolyte solute is dissolved in a definite weight of a given solvent the freezing point of the solvent is lowered by a fixed amount.** This is known as **Raoult's law.** Electrolytes, because of the conditions controlling their degree of ionization, do not display this regularity.

Lowering of the Vapor Pressure of the Solvent.—The vapor pressure of a solvent is depressed in a manner similar to the lowering of the freezing point. Raoult's law covering this phenomenon states that **a molecular weight of a solute dissolved in a definite weight of a solvent will depress its vapor pressure a fixed amount.** The solute must not be an electrolyte or a liquid with a sensible vapor pressure.

Elevation of the Boiling Point.—It is obvious that if a solute lowers the vapor pressure of a solvent it must at the same time raise its boiling point, and with an equal degree of constancy.

Osmosis.—From the medical point of view, this is a most important phenomenon. Life could not continue without it and many medicines would be unable to fulfill their functions. While the pharmacist scarcely ever uses osmosis in his prescription work, many of his preparations act on the patient because of it. The phenomenon results from the tendency of a solute to distribute itself uniformly throughout the solvent. If this diffusion is prevented, the effect, or force, of the diffusing tendency can be both observed and measured. The force that brings about this diffusion is called **osmotic pressure.** In order to determine its presence and magnitude, use is made of a partition that allows the free passage of the solvent molecules, but not those of the solute, between the solution and a surrounding quantity of pure solvent. Such partitions are called **semipermeable membranes.** They can be artificially prepared by precipitating cupric ferrocyanide ($Cu_2Fe(CN)_6$) within the porous wall of an unglazed pottery cup or by forming a collodion bag. Many naturally occurring membranes such as cell walls are semipermeable.

If a semipermeable membrane is placed over an inverted funnel as shown in Fig. 91, the resulting cell filled with a concentrated sugar solution, and the beaker filled with pure water, we have an apparatus that shows graphically how osmosis and osmotic pressure function. The water molecules pass freely through the membrane, but the sugar molecules are

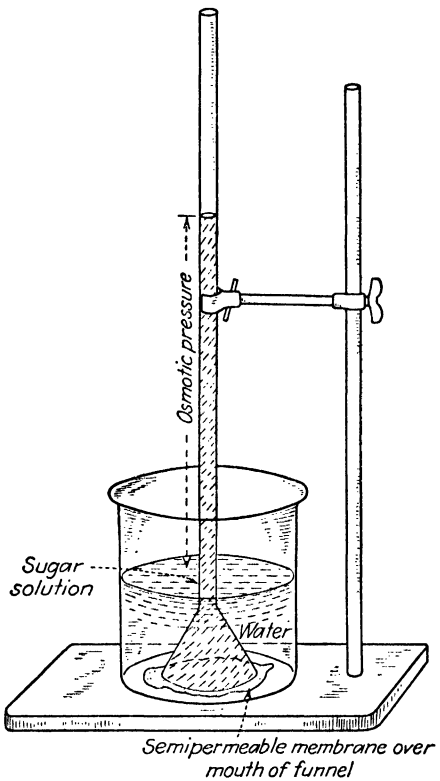

FIG. 91.—The effect of osmosis and its resulting osmotic pressure.

restrained. In order to establish uniformity of concentration, water molecules must pass into the solution at a faster rate than they return. This naturally results in an increased volume within the solution chamber, which is demonstrated by the increase in the height of the column of fluid in the stem of the funnel. Equilibrium is finally reached when the water passes both ways with equal speed, and the level of the solution ceases

to rise. To recapitulate, the passage of the solvent through the membrane is osmosis, and the force exerted as a result is osmotic pressure.

Eutectic Mixtures.—When solutions are cooled sufficiently, crystallization of the solvent takes place. As the pure solvent freezes out of solution, the concentration of the solute increases and the freezing point of the solution lowers. Obviously, continued cooling results in increased concentration of the solute, and eventually it becomes saturated with respect to the solvent. At this point, both solvent and solute crystallize out and do so in the same proportion as they exist in the resulting solution. From then on, there is no change in concentration or temperature. The solution is now called a **eutectic mixture,** and the temperature at which it was produced (its freezing point) is the **eutectic temperature.** The resulting solid, made up of crystals of solute and solvent in a fixed ratio, is a **eutectic.** Advantage is taken of eutectic temperatures in the production of freezing mixtures whose temperatures are much lower than that of ice water. Some of the common mixtures for this purpose are ice and salt, with a eutectic point of −22.4°C., ice and sodium nitrate (−18.5°C.), and ice and calcium chloride (−54.9°C.).

In prescription work a number of compounds, when mixed with certain other compounds in the dry state, tend to form a moist mass that in extreme cases becomes quite fluid. Organic compounds are particularly susceptible to this reaction, which is apparently in no way related to deliquescence but, rather, is considered to be the formation of a partial eutectic, although there is a difference of opinion among physical chemists concerning the validity of this designation as a generally descriptive term. Undoubtedly, the potentialities of a eutectic exist in any of the systems mentioned above, but whether the conditions in a given prescription will ultimately produce one is open to question. Only experiment can give the answer. An eutectic is usually considered to be the intimate mixture of two phases that separates out at the lowest temperature permitting the existence of the parent liquid. In the case of so-called "eutectic prescription" the "eutectic solution" probably never is cooled to the point where a eutectic mixture separates out.

Law of Partition and the Use of Immiscible Solvents in Extraction.—Sometimes it is desirable to remove a solute from solution by the use of a second solvent. This is possible provided that the solute is soluble in both solvents and that the solvents are immiscible with each other. The process is called **extraction** or **extraction by means of immiscible solvents.** It is based on the fact that, when a solute is added to two immiscible liquids in contact with each other, upon agitation of the mixture it will distribute itself between the liquids in the ratio of its solubility in each separately. The commonly used illustration of this is the ether-iodine-water system. If ether is added to a solution of iodine in water and the system agitated, as soon as equilibrium is restored it will be found that the greater part of the iodine is now in the ether layer. Iodine is approximately two hundred times more soluble in ether than in water. It will distribute itself between the two solvents in this ratio. A statement of this fact is known as the **law of partition.** Commonly it is phrased as follows: **A solute will distribute itself between two solvents so that the ratio of its concentration in each is equal to the ratio of its solubility in each.**

In the equilibrium system ether-iodine-water we have this situation: I_2 in water, I_2 in ether. The distribution ratio is CI_2* in ether/CI_2 in water = 200/1. From this a distribution equation follows: CI_2 in ether/CI_2 in water = K. A general equation would be $C_1/C_2 = K$. K is referred to as the **distribution ratio, distribution coefficient, partition coefficient,** or **distribution constant.** Although K is considered to be a constant, there are often measurable deviations from it because of factors such as ionization, molecular associations and dissociations, and chemical reactions.

If equal volumes of ether and water are used in the system under discussion, it is possible to remove practically all the iodine from the water phase in three extractions. Use of this principle is extensive in alkaloidal assay procedures and in the extraction of drugs and volatile oils from plants.

It can be demonstrated mathematically that it is better to extract a liquid with several small portions of solvent rather than one large portion. The total amount of solvent used can

* C = concentration.

be materially reduced and the thoroughness of extraction maintained or improved. Using the general formula $C_1/C_2 = K$ where K is known for the extraction system under consideration, we have $C_1 = \frac{X^*}{\text{cc. of solvent 1}}$, $C_2 = \frac{1 - X}{\text{cc. of solvent 2}}$. Substituting, $\frac{X/\text{cc. of solvent 1}}{1 - X/\text{cc. of solvent 2}} = K$. With values known for all factors except X (the amount of solute extracted by solvent 1), its value is easily determined.

The equation $\frac{C_1}{C_2} = K$ can be used to tell the operator how close he is to theoretically perfect extraction with any particular portion of immiscible solvent in a series. It is of course necessary previously to determine K for the system being used by experiment.

If, in an acid water—ether system, a solute distributed itself so that the ratio $\frac{C_1}{C_2} = 7$, where C_1 is the concentration of the solute in ether and C_2 in acid water, how much solute would be extracted from 100 cc. of acid water solution containing 1 Gm. of solute by three separate 50-cc. portions of ether? In this case, if $\frac{C_1}{C_2} = 7$, then $\frac{X/50}{1 - X/100} = 7$, where X is the amount of solute in the ether and $1 - X$ that remaining in the acid water. Solving, $X = 0.777$ Gm. extracted by the first 50 cc. of ether. $\frac{C_1}{C_2} = 7$. So $\frac{X_1/50}{(0.223 - X_1)/100} = 7$ where X_1 is the amount of solute extracted by the second extraction.

$$X_1 = 0.173 \text{ Gm.}$$

The equation for the third extraction would be

$$\frac{X_2/50}{(0.050 - X_2)/100} = 7.$$

$X_2 = 0.039$ Gm. The sum of the three extractions would be

$$\begin{aligned} X &= 0.777 \text{ Gm.} \\ X_1 &= 0.173 \text{ Gm.} \\ X_2 &= 0.039 \text{ Gm.} \\ \hline \text{Total} &= 0.989 \text{ Gm.} \end{aligned}$$

* X is the amount of solute extracted by solvent 1.

According to the equation $\frac{X/150}{(1 - X)/100} = 7$, one extraction with the entire 150 cc. of ether would yield only 0.913 Gm. of solute.

Ionization.—In chemistry it can be demonstrated that under certain conditions some compounds dissociate into particles carrying electric charges. This is especially true of substances in solution. These charged particles are capable of acting as ferries for electrical currents. The parent substances are called **electrolytes.** The charged particles are called **ions.** If the charge is negative, they are known as **anions.** If the charge is positive, they are called **cations. Ionization** is the name given to the dissociation that furnishes the particles. It will be recalled that while many compounds dissociate they do not all break up with equal thoroughness or to the same degree. The dissociation for some is much more complete at a given dilution than it is for others. Compounds ionizing strongly are called **strong electrolytes. Weak electrolytes** are those which ionize slightly. It must be remembered, too, that a large number of compounds, particularly organic compounds, do not ionize. Their solutions are not capable of conducting an electric current, and so they are called **nonelectrolytes** or covalent compounds.

Conditions that influence the degree of ionization are important. Briefly, these are temperature, nature of the solute, nature of the solvent, and dilution. Knowledge concerning how each of these factors exerts its influence is important to the pharmacist whenever he attempts to control the course of an ionization. It is important also for him to be familiar with the abnormalities produced in the action of solutions of electrolytes because of the irregular increase in particle concentration brought about by ionization. The vapor pressure and freezing points of electrolytic solutions are depressed to an abnormal degree. As the vapor pressure is lowered abnormally, the boiling point must be raised. This rise is as abnormal as the degree of lowering of the vapor pressure. Since the osmotic pressure of a solution is also directly proportional to the number of dissolved particles present, it, too, is abnormal where electrolytic solutions are concerned.

The significance of ionization to pharmacy is great. Many of our medicines would not function unless they were ionized.

Iontophoresis would certainly not be possible. None of the official acids or bases would have value unless their solutions had the properties contributed by either hydrogen or hydroxyl ions, respectively. Many of the salts used in medicine would not function as therapeutic agents unless they could dissociate. The astringent properties of the soluble zinc salts would be lost if no zinc ions could be produced. The antiseptic qualities of certain silver compounds would disappear if the formation of silver ion was not possible. Many clinical tests, valuable in modern diagnosis, would not be usable without ionization.

pH.—In chemical work it is frequently necessary to know the concentrations of hydrogen or hydroxyl ions. The acidity or alkalinity of preparations is generally accepted as being directly proportional to their respective numerical strengths. Solutions are often stable only at one concentration of hydrogen ion or a reaction will not take place unless a definite strength of hydroxyl ions is achieved. There are many other situations that are unsatisfactory for one chemical reason or another if the concentrations of these two important ions are not precisely adjusted. In writing manuals of operation, directions for preservation, monographs on assay procedures, etc., constant mention of hydrogen-ion concentration must be made. The hydroxyl-ion strength can be arrived at by inference if the acid-ion concentration is known.

It would be awkward to express the concentration of either ion in gram ions per liter. The figures required would be many and would involve the use of decimal fractions carried out as far as the fourteenth place. The gram-ion concentration of hydrogen ion in pure water is 0.0000001 gram ion per liter. The gram-ion concentration of hydrogen in very dilute acids can be on the order of 0.000000000001 per liter. Figures such as these might very easily lead to costly errors in calculation. Some less tedious method of expression is highly desirable.

Sörenson, in 1909, devised a satisfactory simplified form of expression for the values based on logarithms. He called it **pH** meaning "potential of hydrogen." Since the total concentration of hydrogen ion increases or decreases, the concentration of the hydroxyl ion is an equivalent amount in the opposite direction. If one value is known, the other is easily calculated; so Sörenson's

system concerns itself directly only with the concentration of the hydrogen ion. It expresses the gram-ion concentration per liter of hydrogen ions as the logarithm of their reciprocals. The gram-ion concentration per liter of the hydrogen in pure water is 0.0000001. Accordingly, the pH of water would be the logarithm of the reciprocal of 0.0000001. The equation is $pH = \log [1/(H^+)]$ where (H^+) stands for the concentration of the ion. In substituting, the formula becomes

$$pH = \log \frac{1}{0.0000001} = \log 10{,}000{,}000 = 7.$$

So the pH of pure water is 7. Since pure water is neutral in reaction, a pH of 7 represents neutrality. Acid solutions have pH values below 7 and alkaline solutions above 7. The total range is between 0 and 14. The relationship between pH values and the concentrations of hydrogen and hydroxyl ions are shown in Table XXII.

TABLE XXII.—RELATIONSHIP BETWEEN pH AND THE CONCENTRATION OF H^+ AND OH^- IONS

	pH	Concentration of H^+, gram ions per liter	Concentration of OH^-, gram ions per liter	p^{OH}
↑	0	1	10^{-14}	14
	1	10^{-1}	10^{-13}	13
	2	10^{-2}	10^{-12}	12
Increasing acidity	3	10^{-3}	10^{-11}	11
	4	10^{-4}	10^{-10}	10
	5	10^{-5}	10^{-9}	9
	6	10^{-6}	10^{-8}	8
Neutrality	7	10^{-7}	10^{-7}	7
	8	10^{-8}	10^{-6}	6
	9	10^{-9}	10^{-5}	5
	10	10^{-10}	10^{-4}	4
Increasing alkalinity	11	10^{-11}	10^{-3}	3
	12	10^{-12}	10^{-2}	2
	13	10^{-13}	10^{-1}	1
↓	14	10^{-14}	1	0

From Table XXII it will be seen that, the stronger the acid, the lower its pH value and that, conversely, the stronger an

alkali, the higher its pH value. As an acid or base becomes weaker, its pH approaches the middle value of 7, which is neutrality.

pH values are now determined by two basic procedures. One is electrometric and requires the use of electrodes and a potentiometer. The other involves the use of colors and so is called colorimetric. Determinations by either are simple enough to be routine for even untrained persons although a comprehension of the principles involved requires some knowledge of chemistry and physics.

Potentiometers for electrometric determinations enable the operator to balance the electric potential of a glass electrode bathed in the unknown solution with that of a standard cell of known potential. As the potential of the glass electrode depends upon the hydrogen-ion concentration of the solution surrounding it, only a simple calculation is needed to convert the potentiometer reading into terms of pH.

Colorimetric procedures are based upon the matching of colors. The usual equipment for this is a series of small glass tubes in which are sealed colored solutions of known pH values. These are the standards. They are prepared by placing a solution of known pH in one of the tubes and then adding a suitable indicator to color it.

Indicators are compounds that vary in color depending on the hydrogen-ion concentration, or pH, of their solutions. The change in color is dependent on the fact that the compound can exist in two interchangeable forms, each having a characteristic color. In the case of phenolphthalein (Ph) the change is ionic. The undissociated molecule is colorless, and the complex ion formed by ionization is red.

$$\underset{\text{colorless}}{HPh} \rightleftharpoons H^+ + \underset{\text{red}}{Ph^-}$$

As acid is added to a solution, the hydrogen is increased, which forces the reaction to the left, tending to form a colorless solution. Addition of alkaline substances, conversely, forces the reaction to the right, producing more colored Ph^- ions. If enough colored ions are liberated, the solution becomes decidedly red. It is apparent that a transition stage must exist between a

completely colorless solution containing largely molecular phenolphthalein and a brilliantly red solution containing chiefly the dissociated indicator. The first perceptible tinge of red appears at a pH of 8.4 and increases in intensity to a pH of 10.5. Further addition of alkali fails to deepen the color. Acids reverse the color change from the maximum red at pH 10.5 to its disappearance at pH 8.4. The pH range of 8.4 to 10.5 is called the transition interval for phenolphthalein. Other indicators have their characteristic transition intervals. These vary from a range as low as 0.2 to 1.8 for acid cresol red to 9.3 to 10.5 for thymolphthalein. Thus it is possible to have a series of colored solutions that will indicate almost any pH value. For the convenience of the analyst the Pharmacopoeia includes a table of pH indicators having a range sufficiently broad for most determinations.

TABLE XXIII.—pH INDICATORS

Indicator	pH Range	Color change	Solvent
Methyl yellow	2.9–4.0	Red–yellow	Alcohol
Bromophenol blue	3.0–4.6	Yellow–blue	3.0 cc. 0.05*N* NaOH
Methyl red	4.2–6.3	Red–yellow	7.4 cc. 0.05*N* NaOH
Bromocresol purple	5.2–6.8	Yellow–purple	3.7 cc. 0.05*N* NaOH
Bromothymol blue	6.0–7.6	Yellow–blue	3.2 cc. 0.05*N* NaOH
Phenol red	6.8–8.4	Yellow–red	5.7 cc. 0.05*N* NaOH
Thymol blue	8.0–9.6	Yellow–blue	4.3 cc. 0.05*N* NaOH
Thymolphthalein	9.3–10.5	Colorless–blue	Alcohol

Indicators for colorimetric determinations of pH such as those listed in Table XXXIII are usually weak acids, although some behave as weak bases. The U.S.P. XII directs that solutions of the basic type and the phthaleins shall be prepared with alcohol as the solvent. Those containing an acid group must first be neutralized with sodium hydroxide (NaOH). The concentration of the indicator solution is normally 0.5 per cent. The solutions should be preserved in tightly stoppered bottles protected from light. Color standards prepared from them should be changed every year or two in order to maintain constancy of tone or intensity.

In each of the remaining tubes of the series a solution of known but different pH is placed and colored with the particular indicator suitable for its degree of acidity. The series now represents a range of indicator colors produced by known

hydrogen-ion concentrations. Samples of the unknown solutions are treated in the same way with the selected indicators. By matching the colors so produced with those in the tubes of known pH values the value for the unknown can be approximately determined. Sets of standards already prepared can be purchased from scientific supply houses. As the tubes are often held in blocklike racks, they are frequently called comparator blocks.

Since students frequently have difficulty calculating pH from H^+ concentration and the converse, hydrogen concentration from pH, the following demonstration problems are offered as guides:

1. Calculate the pH of a solution containing 0.0001 gram-ion equivalents of hydrogen per liter (0.0001*N*).

Solution:

pH = log of the reciprocal of the H^+ concentration

Therefore,

$$\text{pH} = \log \text{ of } \frac{1}{0.0001} = \log \text{ of } 10{,}000 = 4$$

$$\text{pH} = 4$$

The gram-ion concentration of hydrogen could also have been written 1×10^{-4}, in which case the reciprocal would have been $1/(1 \times 10^{-4})$.

2. Calculate the pH of a solution containing 0.000043 gram-ion equivalents of hydrogen per liter (0.000043*N*). Values of this sort are usually expressed as a number multiplied by a power of 10. In this problem, 0.000043 could be written as 4.3×10^{-5}.

Solution:

pH = log of the reciprocal of the hydrogen-ion concentration

Therefore,

$$\text{pH} = \log \text{ of } \frac{1}{0.000043} = \log \text{ of } 23{,}258$$

$$\text{pH} = 4.36$$

Calculation of the hydrogen-ion concentration from pH is illustrated by the next problem.

3. Calculate the hydrogen-ion concentration of a solution having a pH of 4.0.

Solution:

$$pH = \log \frac{1}{H^+}$$

$$4 = \log \frac{1}{H^+}$$

Therefore:

$$\frac{1}{H^+} = \text{antilog of } 4.0 = 10{,}000$$

(Antilog of 4 = 10,000)

H^+ = 0.0001 gram ion per liter.

Buffers.—In pharmacy there are many situations in which it is highly desirable or perhaps absolutely necessary to maintain pH values within certain narrow limits. Some medicinals are stable only if their hydrogen-ion concentration is kept approximately at optimum level. Others function best in one pH range and are relatively inefficient in others. Some cause pain and discomfort when used by the patient unless the pH is properly adjusted. This is particularly true of parenteral solutions, collyria (eyewashes), and nose drops and sprays (nebulae). Other instances in which maintenance of a definite acidity or alkalinity is important could be cited almost without limit.

Under certain conditions this control is automatic. Ionization is self-limiting in a stable situation in which the chemical system involved is not subject to change. A solution of hydrogen chloride in water in which the factors of dilution and temperature are constant reaches an equilibrium between the undissociated hydrogen chloride and its ions.

$$HCl \rightleftharpoons H^+, Cl^-$$

So long as there is no interference due to outside influences, the equilibrium is maintained and the pH of the solution is constant.

Many of the chemical systems dealt with in pharmacy can have little or no freedom from outside influences. They are continually subjected to change. When these changes alter acidity or alkalinity in an unfavorable direction, the pharmacist should make every effort to combat them. Some of his most important aids are buffer solutions. Their function is to resist changes in pH brought about by the addition of some offending

chemical. This they accomplish by combining with it in such a way as to neutralize its effect. Chemicals tending to raise or lower hydrogen-ion concentration do not necessarily find their way into the solution from the outside. They can be formed through natural circumstances within the system. Water carefully distilled in tin stills is neutral. If it is stored in soft glass containers for any length of time, it tends to become alkaline owing to the solution and ionization of the alkaline constituents of the glass.

A good way to maintain a definite pH level against the onslaught of a substance that tends to alter it is to add a protective chemical that withdraws the offending acidic or basic ions by combining with them to form nonionized or slightly ionized but still soluble compounds. Generally this can be done for solutions that are not too strongly acid by adding a salt of a weak acid. Some of the weak acid that produced the salt may be added also. Sodium acetate and acetic acid make one of the popular combinations of this kind. Similarly, for control of solutions on the alkaline side of neutrality, a salt of a weak base, either by itself or with some of the weak base, can be added. An ammonium chloride–ammonium hydroxide mixture would serve.

One of the most important natural buffer systems is found in the blood. Here salts of phosphoric acid play a large part in maintaining the alkalinity of the blood at about a pH of 7.35. As even slight variations on either side of 7.35 result in considerable physical distress, the buffer system must work efficiently at all times in order to preserve health. The part the salts of phosphoric acid play in this necessary biochemical function is simply explained on the basis of ionization. Phosphoric acid, a relatively weak acid, has three series of salts, which in the case of its combination with sodium ionize in the following ways:

NaH_2PO_4 (primary sodium phosphate) $\rightarrow Na^+ + H_2PO_4^- \rightarrow H^+ + HPO_4^{--} \rightarrow H^+ + PO_4^{---}$

Na_2HPO_4 (secondary sodium phosphate) $\rightarrow 2Na^+ + HPO_4^{--} \rightarrow H^+ + PO_4^{---}$

Na_3PO_4 (tertiary or normal sodium phosphate) $\rightarrow 3Na^+ + PO_4^{---}$

The PO_4^{---} tends to form the less ionized HPO_4^{--} by combining with some of the H^+ coming from the water fraction of the solution. This increases the concentration of the OH^-, raising the alkalinity. The HPO_4^{--} ions furnished by Na_2HPO_4 tend to unite with the H^+ from the water and become $H_2PO_4^-$. Again the solutions tend to become alkaline. The $H_2PO_4^-$ from primary potassium phosphate have little tendency toward accumulation of more H^+; instead, they increase the acidity of the solution slightly. Since two of the salts make alkaline solutions and one an acid solution, combinations can be put together that produce definite, comparatively stable pH values and maintain them. Their action is due to the ability of their ions to combine with hydrogen to form slightly ionized substances. In blood, only the primary and secondary phosphates play any appreciable part as buffers. They are augmented by carbonates, hemoglobin, and oxyhemoglobin.

A number of formulas for buffer mixtures have been published. Widely publicized examples are the mixtures of Clark and Lubs found in the Pharmacopoeia XII (see pages 770 to 772). With them pH values from 1.1 to 10 can be established.

Isotonic Solutions.—Solutions dropped in the eyes or the nose or used parenterally by subcutaneous, intramuscular, or other forms of injection, where they come in intimate contact with fluids of the body or tissues bathed by these fluids, can cause great irritation and sometimes do permanent damage if they do not have approximately the same osmotic pressure as the fluids with which they are to mix. Osmotic pressure is due to particles dissolved in a liquid. Its strength depends upon the number of particles per unit of volume. As these increase, so does the osmotic pressure of the solution. When two miscible fluids are mixed, there is immediate uniform dispersion of the dissolved particles of each through the mixture. The osmotic pressure of each solution has been given up in favor of the new pressure possessed by the mixture.

If these solutions had been separated by a semipermeable membrane, the transition would be much slower, from a situation where there were two separate osmotic pressures to one where only a single but new pressure is maintained. To bring about one pressure, the number of the solute particles on each side

of the membrane per unit of volume would have to be equalized by passage of solvent from the side of greatest dilution through to the side of higher concentration. This is, naturally, a slow process and might never be accomplished if there is lack of solvent on the more dilute side of the membrane.

Let us suppose that, instead of a laboratory set up to show the equalization of pressures, a tissue cell is bathed by a concentrated salt solution. The cell wall is a semipermeable membrane, and it will permit the passage of water from the cell to the salt solution in order to equalize the particle concentration per unit of volume on each side so that the osmotic pressures of the enclosed and bathing fluids will be the same. As a result of this fluid transfer, the cell loses water and shrinks. If the shrinkage continues or becomes permanent, the functions of the cell are impaired or completely destroyed. The reduction in activity is frequently accompanied by pain experienced by the patient. A bathing fluid less concentrated with solute particles than the cell causes a flow of diluting solvent into the latter, with the result that the cell swells. The diluting process may even fill it to the point of bursting. Pain may again be the accompanying phenomenon. These are small-scale examples of the situations that arise when solutions having osmotic pressures different from body fluids are mixed with them. This is one of the main reasons why injections sometimes hurt or smart until absorption is complete.

Solutions which are lower with respect to osmotic pressure than those with which they are to be combined are called **hypotonic** solutions. Solutions which are higher are called **hypertonic.** Solutions which, for all practical purposes, are equal to those with which they are to be mixed are called **isotonic.** The manufacture of isotonic preparations is an essential part of pharmacy. Their use in medicine makes for more comfortable parenteral injections or dropper instillations.

To make one solution isotonic with another it is first necessary to have a basis for comparing the values of their respective osmotic pressures. This can be done by comparing the freezing points of each. Like osmotic pressures, freezing points of solutions are dependent on the number of particles contained. An increase in the number of particles lowers the freezing point,

the amount of depression being proportional to the number added. Blood freezes at −0.56°C. To make a salt solution isotonic with blood, enough sodium chloride (NaCl) is added to lower its freezing point to −0.56°C., indicating that its active particle concentration is now approximately that of the blood. The two can be mixed with a minimum of fluid exchange through cell walls so that an injection of the solution would be much more comfortable for the patient. Tables have been prepared giving the freezing points of some dilute solutions having a possible use as parenteral injections or instillations, but they are only fragmentary in scope and so are of little real value. What is really necessary is that the freezing points of usable concentrations of the new drugs constantly appearing on the market which might find their way into isotonic solutions should be continuously determined and recorded. Tables so extended would furnish the pharmacist with sufficiently complete data to be worth while.

Perhaps an easier way to calculate how much of a given substance will be required to give one solution approximately the same particle concentration or osmotic reference pressure as another is the one publicized by Nicola[1] in 1921. It has subsequently found its way into a number of texts. The osmotic pressure of the solution to which the new solution is to be added must be known, or at least must be given a value. This is necessary so that the new solution can be built up to an equivalent value. The first requirement is easily met in medicine, for there are comparatively few fluids in the body with which injections or instillations can be mixed. It is necessary only to determine their osmotic pressures and to state these in terms that can be met by the new solution. The terms are called **osmotic factors** or **isotonic factors.** The problem then is to duplicate in the new solution the osmotic factor of the body fluid or other liquid with which it is to be mixed.

Blood has an osmotic pressure equivalent to that of a sodium chloride solution containing about 0.85 Gm. in each 100 cc.* The osmotic factor of blood is based on this relationship and is arrived at in the following calculation:

[1] F. NICOLA. *Giorn. farm. chim.* **70,** 57 (1921).

* The U.S.P. XII value is 0.9 Gm. per 100 cc.

$$\text{Osmotic factor} = \frac{0.85\ (\text{Gm. of NaCl in 100 cc.}) \times 1.86\ (\text{dissoc. const. of NaCl})}{58.5\ (\text{molecular weight of NaCl})}$$

The value for this equation is 0.027026. All solutions for injection into the blood stream must possess approximately this osmotic factor in order to be isotonic. Since the value is for blood, it is sometimes referred to as the *serum isotonic factor*.

To arrive at the osmotic factor for any other solution it is necessary only to know the amount of sodium chloride required to give a unit volume of water an equivalent osmotic pressure. Substitute this weight in grams in the formula above for the 0.85, and solve. Tear secretions, for example, freeze at about −0.80°C., corresponding to the freezing point of a salt solution containing 1.4 Gm. of sodium chloride in 100 cc. of water. The osmotic pressures of these solutions are nearly identical; so the osmotic factor of one would be the osmotic factor of the other. Therefore, substituting 1.4 Gm. in the formula under discussion, we have

$$\text{Osmotic factor} = \frac{1.4 \times 1.86}{58.5} = 0.04450$$

which is the osmotic factor for either tear secretions or a salt solution of equivalent concentration. Any solution whose particle concentration per unit of volume is such as to furnish this value will be isotonic with either. Solutions for instillation into the eyes should be prepared so that they possess this factor.

One difficulty of Nicola's[1] method is the use of dissociation constants. They are not always readily available, and they vary with conditions. Husa[2] has simplified this problem in a practical way by assuming complete dissociation in most instances.[3] Thus, when sodium chloride is involved, every molecule is assumed to form two ions. Its dissociation value is 2. Organic molecules that do not dissociate have 1 for their values. Weak electrolytes such as boric acid are treated as nondissociating organic compounds.

[1] F. NICOLA. *Giorn. farm. chim.* **70**, 57 (1921).

[2] W. J. HUSA and OSCAR A. ROSSI. *J. Am. Pharm. Assoc. Sci. Ed.* **31**, 270–7 (1942).

[3] For other simplified calculations refer to the paper by J. M. Wills, *J. Am. Pharm. Assoc. Pract. Pharm. Ed.* **5**, 99–106 (1944).

Knowing the osmotic factor of the fluid to be treated is only part of the picture, for it simply tells the manufacturer the value to which he must adjust his solution to make it isotonic with the fluid. He must next calculate the osmotic factor of his solution before anything is added to make the adjustment. Suppose he wants to prepare a 1 per cent solution of cocaine hydrochloride that will be isotonic with the blood. As a beginning, he knows the osmotic factor to be 0.027026. He next determines, by the same formula that gave him this value, the osmotic factor for the 1 per cent cocaine hydrochloride solution.

$$\text{Osmotic factor} = \frac{1\ (\text{Gm. of cocaine HCl in 100 cc.}) \times 1.5\ (\text{dissoc. const.})}{339.6\ (\text{molecular weight cocaine HCl})} = 0.004446$$

This indicates that there is a great difference in osmotic factors between blood and the cocaine solution which will have to be adjusted by adding a salt such as sodium chloride to the latter. The difference in factors to be made up, 0.022580 (0.027026–0.004446), constitutes a new osmotic factor known usually as the *differential osmotic factor*. In this problem, if the manufacturer wishes to use sodium chloride to build up the particle concentration of his cocaine hydrochloride solution so that it has the same tonicity as the blood, he will do it just as though he were preparing a simple solution of sodium chloride alone having an osmotic factor the same as the differential osmotic factor, namely, 0.022580.

Nicola's formula, which shows how much sodium chloride to add to achieve this result, follows:

$$\text{Number of grams of NaCl to be added} = \frac{0.022580\ (\text{differential factor}) \times 58.5\ (\text{molecular weight NaCl})}{1.86\ (\text{dissociation constant NaCl})} = 0.705$$

Adding 0.705 Gm. of sodium chloride to every 100 cc. of 1 per cent cocaine hydrochloride solution will raise the osmotic pressure to that of the blood and so make it isotonic.

STERILIZATION

Preparations for certain uses must be sterile, *i.e.*, free from all living organisms. This is true for most solutions administered parenterally, for surgical dressings, and for sutures. It is frequently true for apparatus and containers used in the manu-

facture of medicinal substances, for hypodermic needles, syringes, rubber tubing, and stoppers, and for many other items.

Some of these can be safely sterilized in a free flame; others decompose under the influence of even low temperatures. Some can be sterilized in a moist atmosphere; others must be kept dry. This creates a problem in that one procedure cannot serve for all the conditions under which sterilization must be accomplished. Therefore, a number of methods have been devised so that by proper selection almost any substance, however delicate or sensitive it may be to special influences, can be rendered germ free.

Several of these techniques have been made a part of the Pharmacopoeia and the National Formulary. They are called process *A*, *B*, and so on. All but two in the Pharmacopoeia and one in the National Formulary make use of heat in some form as the principal sterilizing agent. The first exception is a filtration procedure in which the bacteria are removed; in the second, sterility is achieved through aseptic manipulation. In process *A*, direct contact with a free flame is used. Only those materials uninjured by high heat can be so treated. Platinum wires, needles, tweezer tips, forceps, and spatulas are quickly sterilized by heating to redness in the flame. Heavier, thicker objects such as slabs, mortars, plates, and metallic orifices of bacterial filters should have their entire areas in contact with the direct flame for at least 20 sec. The procedure is not recommended for slides and cover slips, glass rods, and the lips of glass containers because of the danger of cracking.

Glassware is usually sterilized by process *B*, which is exposure to the dry heat of an oven. This is the procedure ordinarily used to sterilize any empty container that is to be kept on hand for future use. Every item must have been carefully cleaned previously and must be free from organic matter. This precaution is observed in order to prevent contamination by charring. It is always excellent technique to clean any equipment or container before sterilizing. One of the common cleansing procedures is to boil the objects not less than 10 min. in a soap solution and follow this by a careful rinsing and another boiling in a 0.1 to 0.3 per cent acid solution. Hydrochloric or nitric acids are the acids ordinarily used. Special solvents may

be required in order to remove the more adherent organic matter. In any procedure the final step is a thorough rinsing with distilled water.

The objects to be sterilized are placed in a suitable oven, ordinarily maintained at a temperature between 160 and 190°C. for at least an hour, preferably two hours. To avoid cracking of glassware, both the heating and the cooling should be done gradually. If it is desirable to keep a substance sterile for any length of time after heating, it should be carefully wrapped in paper or placed in closed containers before sterilizing. There is always the danger of charring cotton plugs in flasks and test tubes and paper wrappings. In order to prevent this, when they are present the temperature should never be allowed to rise beyond 190°C. Any material not injured by greater heat can be sterilized in a shorter time by increasing the temperature to 200°C., or more. As the temperature increases, the sterilizing time decreases proportionally; conversely, the lower the sterilizing temperature, the longer the time required. For example, sulfanilamide is decomposed by high heat; therefore, it is sterilized at 140°C., but the time required is 4 hr.

The most satisfactory procedure for using heat is process *C*, in which sterilization is achieved by means of steam under pressure, in the comparative absence of air. Steam under pressure is hotter by several degrees than the same vapor at atmospheric pressure. The increase in temperature is proportional to the increase in pressure. Bacteriologists have determined that moist heat between 115 and 127°C. generally destroys spores as well as vegetative forms of bacteria at one fairly short exposure. The pressures required to give this range of temperatures together with the corresponding periods of time required for adequate sterilization are 10 lb. pressure (115.5°C.) for 30 min., 15 lb. pressure (121.5°C.) for 20 min., and 20 lb. pressure (126.5°C.) for 15 min. The pressures are reached by using either an autoclave or an ordinary steam-pressure kettle such as is found in the kitchen. Time must be allowed after the desired pressure has been reached to ensure uniform heating of the centers of the materials or substances being sterilized.

Process *D* also makes use of moist heat, but not under pressure. Either free flowing steam or boiling water is the sterilizing

medium, and so the temperature does not exceed 100°C. It should be remembered that at high altitudes, where the atmospheric pressure is less than 760 mm. of mercury, the temperatures of both steam and boiling water are less than 100°C. More certain results are achieved by exposing the material to the heat for 30 min., or more, on three consecutive days. During the intervals between exposures the material is kept in an incubator at body temperature or at room temperature. This repetitive treatment is called **fractional, intermittent, interrupted,** or **discontinuous sterilization** or **Tyndallization.**

If boiling water is used, its effectiveness can be increased by adding 1 to 2 per cent of sodium carbonate, 5 per cent of phenol, or 2 to 3 per cent of cresols. The instruments, rubber stoppers, tubing, needles, or other articles or materials being treated should be entirely submerged.

Substances injured by the temperature of boiling water can be treated by process *E*, or **inspissation,** which is a modification of process *D*. The temperature of the sterilizer is kept at the highest point compatible with unaltered composition of the material being heated. This is usually between 60 and 80°C. It is recommended that a bacteriostatic agent shall be added to medicinal preparations being treated by this method, in concentration sufficient to prevent the growth of all microorganisms in the material. Even then the process is not guaranteed, and process *F* is suggested as an alternate procedure wherever practical.

Process *F*, which is called **bacteriological filtration** (see pages 505 to 507), is used principally for solutions whose active ingredients are injured by heat. Such liquids are filtered through a sterile filter of the Pasteur-Chamberland type. The filtrate generally is bacteria free, but the results are not certain; so a bacteriostatic agent should be added as directed for process *E*.

The high temperatures of salt or oil baths are employed as a means of sterilizing in process *G*. Saturated solutions of sodium or ammonium chlorides boil at a temperature about equal to that obtained in an autoclave between 10 and 15 lb. pressure. Boiling light mineral oil is excellent for sterilizing instruments of which the edges or finish must be protected or for catheters which must be lubricated.

It is possible, by using careful aseptic technique and sterile containers, solvents, etc., to prepare some substances in a sterile condition, thus obviating the need for subsequent heating. This is called process *H* or **aseptic manipulation** and is used for materials damaged by ordinary processes of sterilization. It is to be used only when no other procedure will apply. The materials are to be labeled so as to show the date of preparation and the notation "Prepared by aseptic manipulation. Keep in a cool place and use within two (2) days."

STUDY QUESTIONS

1. Define the term *solution.*

2. How do solutions differ from mixtures?

3. What determines which component of a solution will be called the solvent?

4. Are fogs solutions of gases in gases?

5. How could you prepare a solution of aspirin in carbonated water without using already prepared siphon water or the equivalent?

6. Cite examples other than those in the text of fluids only partly miscible in each other.

7. Write the equation that illustrates the solution of zinc in hydrochloric acid. How can you remove the hydrogen formed?

8. What is meant by dynamic equilibrium?

9. How can one hasten the solution of such slowly soluble substances as sugar?

10. Give an example of a molar solution having (*a*) the same concentration as a normal solution, (*b*) two times the concentration.

11. If the distribution ratio $C_{CHCl_3}/C_{acid\text{-}H_2O} = 4.25$, how much solute will three extractions of 25 cc. of $CHCl_3$ each remove from 50 cc. of acid water containing 2 Gm. of solute?

12. Calculate the pH of a solution having a H^+ concentration of 0.000076 gram ion per liter.

13. Calculate the hydrogen-ion concentration for a solution with a pH of 2.35.

14. What other buffer systems are found in the body besides that in the blood?

15. Describe how you would proceed to make a 1 per cent cocaine solution isotonic for hypodermic injection.

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CHAPTER XIII

THE COLLOIDAL STATE

The sum of knowledge in chemistry has grown to such proportions that it has become necessary to divide it into a number of specialized branches. One of these is **colloid,** or **colloidal, chemistry.** This deals with substances in the **colloidal state.** A substance is said to be in the colloidal state when it exists as a dispersion of submicroscopic particles throughout some dispersing medium. Considerable variation in size of the submicroscopic particles is possible without loss of colloidal properties. The principal requirements are that they must be larger than the molecules and ions found in solutions and smaller than the aggregates in the most finely divided suspensions. In an effort to be more precise, chemists have suggested that particles smaller than one millimicron ($m\mu$)* are not colloidal since their presence tends to cause the mixture to behave as a true solution in that properties such as the vapor tension, freezing point, and osmotic pressure of the dispersion medium are altered. Particles larger than 100 to 200 $m\mu$ are made visible by the more powerful microscopes and so leave the colloid field. The dimensional boundary is purely arbitrary and not too effective. It is well to remember W. Ostwald's teaching that there is no sharp line of demarcation between suspensions, colloids, and solutions. Instead, the transition is gradual, and overlapping occurs. Thus, a colloid may have properties in common with either a suspension or a solution, or both.

The colloidal state is not peculiar to any one group of substances. Some can be made colloidal more easily than others. Gelatin, for example, becomes colloidal upon mixing with water. Gold, on the other hand, requires treatment with special apparatus and methods in order to change its ordinary forms into the colloidal state. Water, dissolved in the proper organic solvent and cooled below its freezing point, becomes colloidal ice.

* $1\ \mu = 0.001$ mm. $= 10^{-6}$ M; $1\ m\mu = 0.000001$ mm. $= 10^{-9}$ M.

Classification of Colloid Systems.—Colloids can be formed with any of the three states of matter acting as the dispersing medium. The commonest are those in which a liquid is the dispersing medium. Many others have either a gas or a solid as the continuous phase, and the dispersed substance may be a gas, liquid, or solid. Since all gases are soluble in each other, there are no colloids consisting solely of a gas dispersed in a gas. Babor and Lehrman[1] have prepared an informative table illustrating the structure of colloids (see Table XXIV).

TABLE XXIV.—CLASSIFICATION OF COLLOIDS ACCORDING TO BABOR AND LEHRMAN

	Dispersion medium	Disperse phase	Examples
1	Gas	Gas	Noncolloidal (all gases are soluble in each other)
2	Gas	Liquid	Clouds, fogs, mists
3	Gas	Solid	Smokes, volcanic dust
4	Liquid	Gas	Foams, such as whipped cream
5	Liquid	Liquid	Emulsions, such as milk
6	Liquid	Solid	Colloidal oxides, sulfides, etc. Starch suspension, colloidal dyes, etc.
7	Solid	Gas	Meerschaum, pumice stone, white hair
8	Solid	Liquid	Jellies, gels, cheese
9	Solid	Solid	Ruby glass, precious stones

Types of Colloidal Dispersions.—Colloidal dispersions are generally known as **sols.** If water is the dispersion medium, the colloid is a **hydrosol.** If alcohol is the dispersion medium, we have an **alcosol,** and so on. If a jelly is produced when a hydrosol is partly evaporated, it is called a **hydrogel.** Upon complete evaporation the solid residue becomes a **gel.** The process of transforming sols into gels is also known as **coagulation** and **flocculation.** In elementary discussions, colloids are usually classified in two large divisions, suspensoids and emulsoids. **Suspensoids** are those colloids which are precipitated by small amounts of electrolytes and which cannot be returned to the

[1] JAMES ALBERT BABOR and ALEXANDER LEHRMAN. "General College Chemistry," The Thomas Y. Crowell Company, New York, 2d ed., 1940, p. 443.

colloidal state by restoration of the dispersion liquid after it has been evaporated. Suspensoids are known also as lyophobes or hydrophobes (water-fearing). **Emulsoids** are stable toward electrolytes and when evaporated can be returned to their original state by restoration of the dispersion liquid. They are also known as **lyophyls** or **hydrophyls** (water-loving). They are designated in still another way, namely, reversible colloids, because they can be restored to their original state, after being evaporated to dryness, by addition of the dispersing fluid. In contrast, suspensoids are known as irreversible colloids.

Colloidal nomenclature is still not completely standardized. The connotation of certain terms is in need of clarification in order to facilitate the accurate transfer of ideas among research workers in the field.

Importance of Colloids in Medicine and Pharmacy.—The body is made up of countless thousands of living cells, each of which is colloidal in nature. The chemistry of these cells is directly a part of practically every life process. Their proper functioning is necessary for health. Any dysfunction results in unhealthful disturbances in chemical equilibriums. Medical measures to correct such disturbances must be based on a knowledge of the colloid chemistry of the body. Even in correcting ailments due to chemical shifts in the body, which are not colloidal in nature, medicines in colloidal form are often more effective than those which are not. Hyperacidity, for example, is treated most efficiently with colloidal magnesium and aluminum compounds. These function, not as chemical neutralizers, but as colloidal absorbents. The value of colloids in the pharmaceutical aspects of medicine has only begun to be evident.

Properties of the Colloidal State. *Diffusion.*—Colloids have the ability to diffuse. They do not diffuse through semipermeable membranes with the same facility as noncolloidal particles of true solutions. Advantage is taken of this fact in separating certain colloids from contaminating molecules and ions by **dialysis.** In this process the colloid is placed in a parchment bag, which is immersed in pure water. The colloidal particles cannot pass through the parchment, but the molecular or ionic contaminants can. This fractional diffusion can be

carried to the point of almost complete separation of the colloid from its impurities by frequent changing of the water in the bath. Semipermeable membranes other than parchment are quite satisfactory.

Tyndall Effect.—The path of a beam of light passing through a medium containing dispersed particles of proper size is made visible because the rays are scattered as they collide with the particles. An illustration of this is light entering a darkened room through some tiny aperture. Dust particles, invisible

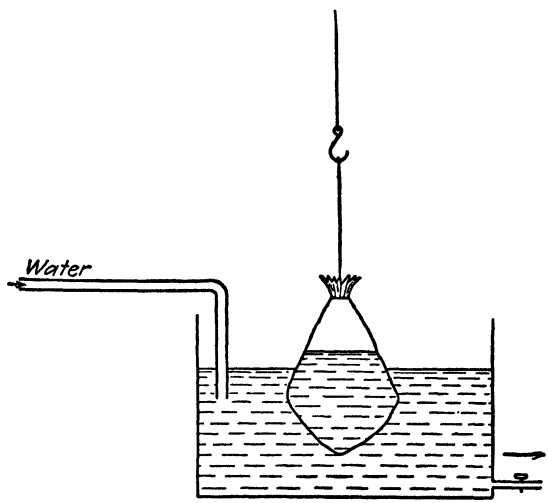

FIG. 92.—Dialyzing apparatus in which the bathing solution is constantly changing.

in the well-lighted room, become visible now as bright flashes in the path of the beam. Some of these particles are colloidal in size. Illumination in this manner of the path of a beam of light is called the **Tyndall effect,** after its discoverer. The ultramicroscope takes advantage of the phenomenon. A strong beam of light is focused on a cell filled with a colloidal dispersion. The flashes of refracted and scattered light formed by the collisions between the light rays and colloidal particles can be caught and magnified by a microscope focused on the cell against a dark background. It is the refracted light rather than the particles that is observed. Since true solutions do not show the

Tyndall effect, it can be used to differentiate between them and colloids.

Brownian Movement.—Fluid colloids exhibit **Brownian movement.** Brown, a botanist, observed that grains of pollen suspended in water were in a constant state of agitated motion. A grain would move in a straight line for a very short distance and then suddenly alter its direction. The result was a series of erratic, rapid, zigzag paths. Colloidal particles tend toward the same type of irregular motion, which can be easily observed with an ultramicroscope. It is caused by the impact of the

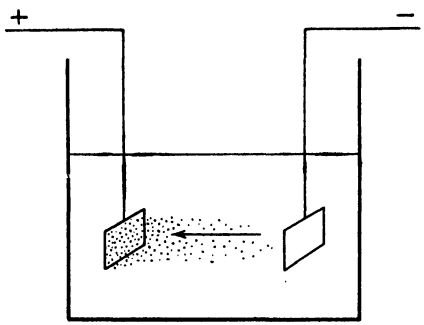

FIG. 93.—Cataphoresis, showing migration of colloidal arsenious sulfide particles to the anode.

molecules of the dispersion medium against the colloidal particles. The collisions keep the particles in a constant state of motion and hence tend to prevent settling or sedimentation.

Electric Charge.—Generally, lyophobic colloidal particles are electrically charged. The charge may be either positive or negative. One of the commonly used proofs of this is the effect produced by the passage of an electric current through colloidal arsenious sulfide. Under the impact of the current the yellow colloid moves to the anode, where it loses its negative charge and precipitates. The fact that all the colloid moves shows that every particle is charged alike. The repelling effect of like charges helps preserve the integrity of the colloid. **Cataphoresis** is the name given to the movement of a colloid to the pole of opposite sign.

One explanation for the charge is the adsorption of specific ions from the dispersion medium. Frequently these are either

hydrogen or hydroxyl ions. Adsorption of the former gives the colloid a positive charge. Adsorption of the latter has the opposite effect. The metallic sulfides and the metals themselves are usually negatively charged, and metallic oxides ordinarily carry positive electricity.

Lyophilic colloids can exist with or without an electric charge. Frequently lyophils are amphoteric, and so the hydrogen-ion concentration of the dispersion regulates the type of charge adsorbed. In a strongly acid medium hydrogen ions would be adsorbed. An alkaline medium would produce a negative colloid. There is a pH at which the colloid would have no charge. This is the **isoelectric** point.

Precipitation by Electrolytes.—It frequently is possible to precipitate colloids by adding small quantities of electrolytes. Colloidal arsenious sulfide precipitates when treated with minute quantities of silver nitrate. The reaction is not stoichiometric, for there are no standard quantities of each required. Factors such as age, temperature, and method of preparation of the colloid seem to regulate the amount of silver nitrate necessary for precipitation. In no case does it require anywhere near the silver salt necessary for a double-decomposition reaction. Colloids can usually be precipitated, too, by the addition of high concentrations of ions whose charges are opposite that carried by the colloid. These remove the stabilizing action of mutually repelling charges on the colloidal particles, and coagulation results. Colloidal dispersions of silt in river water are precipitated at the river mouth in the form of a delta by the action of the electrolytes dissolved in the sea. Bivalent and trivalent ions apparently are more effective precipitants than monovalent ions. Advantage is taken of this fact in water-clarification projects using the trivalent aluminum ion of aluminum sulfate.

Protecting Colloids.—Unstable colloids may sometimes be prevented from coagulating by a stable **neutral colloid** or one carrying the same kind of electrical charge. These are called **protective colloids.** An illustration of the principle of protection is the use of gelatin to protect suspensoids of silver salts in the manufacture of photographic films. Potassium bromide is mixed with silver nitrate in the presence of about one

per cent of gelatin. Instead of the usual precipitate of silver bromide a colloidal dispersion is formed. Probably the particles of silver bromide are coated with a thin film of gelatin, which prevents their coalescence. Colloidal silver iodide used as an antiseptic in medicine is stabilized with gelatin in the same way.

Adsorption.—Adsorption is the adherence of ions, atoms, or molecules to surfaces. It differs from absorption in that the latter requires penetration into the absorbing body as in the flow of water into a sponge or the taking up of fluid by some other porous solid. It is not always easy to say where adsorption ceases and absorption begins. But we do know that adsorption is always a surface phenomenon and is dependent on surface forces.

Colloids, because of the huge surface they expose in comparison with their mass, are frequently capable of tremendous adsorption. This power to adsorb may be **selective.** Certain emulsions are produced because the emulsifying agent is adsorbed on the surface of one of the immiscible liquids, thus forming stable droplets that have a minimum coalescing tendency. Adsorption is probably responsible for the efficiency of some catalysts. It enables them to bring the reacting substances together in concentration on their surfaces. Adsorption is used as a means of removing many colored impurities from liquids. The liquids are filtered through selective adsorbents that remove only the colored contaminants.

Color of Colloidal Dispersions.—Colloids are often attractively colored. The possession of color is due to the absorption of certain wave lengths of light and the scattering of others by the colloidal particles. The dimensions of the particles determine the selectivity of absorption by which dispersions of the same substance may have different colors. For example, gold hydrosols may be blue, red, violet, or even green, depending on the particle size of the disperse phase. Ruby glass contains colloidal gold. If selenium is used instead of gold, the glass becomes red. Certain precious stones owe their color to small amounts of colloidal impurities. The deep blue of some lakes is undoubtedly due to colloidally dispersed material in the water. Colloidal dust causes the sky to become dark blue.

The Production of Colloidal Systems.—Since colloids occupy a middle position, from the standpoint of particle size, between

the coarse particles and molecular dispersions, there must be two basic ways in which they are produced. These are (1) the comminution, or subdividing, of coarser particles, called **dispersion methods;** and (2) the condensing, or aggregation, of ions, atoms, or molecules into particles of colloidal dimensions, called **condensation methods.**

Dispersion Methods.—These ordinarily are purely physical procedures involving no chemical reactions. Grinding in a colloid mill is typical. When ground to an impalpable powder and mixed with a dispersion medium, dry substances will form colloids. Milling in this fashion produces a polydisperse system containing both submicroscopic and microscopic particles. Hauser[1] proposes, therefore, that such machines shall be called dispersion mills instead of colloid mills.

Dispersion is sometimes brought about or facilitated by **peptization.** Peptization involves treating finely divided solids, usually precipitates, with some reagent that causes them to break up into particles of colloidal size. The reagent might be an electrolyte; for example, a small quantity of ferric chloride changes a precipitate of hydrated ferric oxide into a stable sol. Or it could be a liquid, as in the formation of a gelatin hydrosol by the simple addition of water to the gelatin. Water in this instance is the **peptizing agent.** It functions by **solvating** (hydrating) the gelatin particles.

Metals can be colloidally dispersed by means of the Bredig method. If two electrodes of the metal are dipped into water, the passage of an electric current through the electrodes will create an arc. Particles of the metal of colloidal size will split off and remain suspended in the water. Colloidal gold is prepared in this way. Some chemists consider this method a combination of dispersion and condensation procedures. They reason that a part of the metal separates as a vapor, which is condensed as a colloidal dispersion. Pure water is not so satisfactory for the dispersion medium as a liquid containing traces of an electrolyte. Liquids other than water should be used for metals above hydrogen in the electromotive series.

[1] E. A. HAUSER. "Colloidal Phenomena," McGraw-Hill Book Company, Inc., New York, 1939, p. 63.

Condensation Methods.—Chemical reactions that cause ions, atoms, or molecules to coalesce into particles of colloidal dimensions are used in these methods. Unless dilute solutions of the reacting materials are used, there is danger that particles large enough to precipitate will be formed. This phenomenon leads to the possibility that the first stage of precipitation is the formation of a colloid. Oxidation, reduction, double decomposition, hydrolysis, and alteration of solvent will all produce colloids when properly controlled. Examples are

1. Reduction, the use of hydrazine hydrochloride in the production of a gold sol.

2. Oxidation, the formation of colloidal sulfur by the action of air on a solution of hydrogen sulfide.

3. Double decomposition, the formation of colloidal lead sulfide by the action of hydrogen sulfide on colloidal lead hydroxide.

4. Hydrolysis, the formation of colloidal ferric hydroxide by the action of hot water on ferric chloride.

5. Alteration of the solvent, water poured into an alcoholic solution of an oil will cause the formation of colloidal particles of the oil.

STUDY QUESTIONS

1. Explain the difference between (*a*) a colloid and a solution, (*b*) a colloid and a suspension.

2. What is the value in meters of a micron? A millimicron?

3. Classify colloids according to Babor and Lehrman.

4. Explain the difference between a suspensoid and an emulsoid.

5. Why are colloids important in pharmacy?

6. List four properties of the colloidal state, and explain each.

7. How should you prepare a gold sol by the Bredig method?

8. Explain why the deep blue of lake water is of interest in this chapter.

9. Does a colloid mill produce a perfect colloid? Explain your answer.

10. How does adsorption aid a catalyst?

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CHAPTER XIV

EMULSIFICATION AND EMULSIONS

"The word emulsion comes from two Latin terms, *e* out and *mulgere* to milk, *i.e.*, to milk out, to drain out. This meaning denotes action such as the act of milking. Hence the verb denotes a process rather than a product."[1] The word *emulgent*, of the same origin, has been used in early works upon anatomy and physiology in describing the functions of the veins, arteries, and urinary vessels. Emulsion and *emulgere* have also been put to interesting literary and social uses. The "indulgences" of historical fame have been referred to as "emulgences." In all such cases the idea of action has been expressed.

Early Definitions.—In early medical and pharmaceutical literature only natural emulsions were thought of, namely, those which were prepared by mixing, grinding, or triturating seeds and gum resin, such as almond seed and asafetida, with water. In other words, milklike liquids were classed as emulsions.

In 1611 Cotgrave[2] defined emulsions as follows: "An emulsion; any kind of seed, etc., brayed in water, and then strained to the consistence of an almond milke; also any kind of creame, or milkie humor." A century or more later Quincy[3] said, "Emulsion, signifying milking out, is a form of medicine made by bruising oily Seeds and Kernels, and drawing out their Substances with some liquor that becomes thereby milky—and these are generally of the emollient kind." More than a century later Ogilvie[4] defined an emulsion as "a soft liquid remedy of a colour and consistence resembling milk; any milk-like mixture

[1] *Pharm. Arch.* **8**, 25 (1937).

[2] R. Cotgrave. "A Dictionary of the French and English Languages," 1611.

[3] J. Quincy. "A New Physical Dictionary," 1719, p. 131.

[4] J. Ogilvie. "The Imperial Dictionary, English, Technological, and Scientific," 1856.

prepared by uniting oil and water by means of another substance, saccharine or mucilaginous."

In an examination of the definitions of emulsions of the past two or three centuries, one is impressed with the fact that the so-called "natural," or "seed," emulsions were known and used for a considerable period prior to the advent of the so-called "artificial emulsions." It would be interesting to know who was the first to observe that a fixed oil can be made into an emulsion by mixing it with a gum and applying the proper technique.

Modern Definition.—An emulsion may be defined as a two-phase system of immiscible substances, usually liquids such as water and a fixed oil, fat, resin, or wax, one of which is reduced to a fine state of subdivision and dispersed in the other. The dispersion of one of these substances in an emulsion system is effected by severe agitation of some kind. In pharmacy, this is done by shaking, by rapid trituration in a mortar, or by a machine. The disperse phase of such a system is only temporary unless a third substance, called the emulsifying agent, has been added prior to the agitation. Perhaps the best-known emulsifying agent in pharmacy is acacia. Therefore, to get a stable emulsion of an oil, *e.g.*, cod-liver oil, three substances are necessary, namely, water, oil, and the emulsifying agent. Moreover, for good emulsions, favorable proportions of each of these ingredients are necessary and the agitation must be sufficiently vigorous to cause dispersion of the oil into globules of microscopic size. Emulsions of this type have a milklike appearance varying from a thin to a thick liquid, even to the consistency of mayonnaise.

Nature produces several interesting emulsions such as milk, egg yolk, protoplasm, and the latex of plants. The brain has been referred to as an emulsion. The chyle too has an emulsion-like appearance. Gum resins, such as asafetida, are known to us as drugs in the form of hard lumps or dry powders. In the fresh state they were the milky juices of the plants from which they came. When these dry gum resins are ground up with water, they are rehydrated to their original milklike appearance. For this reason, gum resins are sometimes referred to as *natural emulsions*. Being gum resins, it is believed that, upon mixing

them with water, the gum forms a solution, which in turn suspends the dispersed resin particles.

Egg yolk is about 23 per cent oil. The oil is dispersed in protein matter. Protein substances in the latex of the rubber plant are credited with causing the emulsification of the insoluble rubber present.

Milk has been referred to as the most nearly perfect of the natural emulsions, but even milk is not permanent for long. It is composed of about 3.5 per cent butterfat and about 3.3 per cent casein. The latter aids in emulsifying the former in a large proportion of water. Milk may be diluted almost indefinitely without oily separation; and although it may "cream" upon standing, the creamy layer can easily be diffused again by shaking. The commonly known pharmaceutical emulsions do not behave so well in this respect. All will cream upon standing and, if diluted too much, show separation of oil globules in a short time.

Emulsion Phases.—The **dispersed phase** has been referred to as that phase of an emulsion which exists in fine globules of microscopic sizes. It is also called the **internal** or **discontinuous phase.** The other phase of an emulsion system is called the **external phase, continuous phase,** or **dispersion medium.** The emulsifying agent is considered by some to be the **intermediate** or **third phase.** However, in the case of gums such as acacia that are soluble in water, it is doubtful whether it should be considered as being a separate phase. While the emulsifying agent may be just as important in the formation of pharmaceutical emulsions as either the oil or the water, it will be referred to merely as the emulsifying agent in this chapter.

Modern Theories of Emulsification.—Much attention has been given to the theory of emulsification by physical chemists during the past thirty years. Prior to the time when the chemists became interested in the problem, pharmacists were supposed to know all that there was to know about emulsions. Their knowledge of emulsions was, however, of a practical nature and did not go far toward explaining the theory of emulsions and emulsification. It should be appreciated that prior to about 1900 emulsion was a term associated with a medicine of some kind. Since then it has come to mean much in industry

and technology. Medicinal emulsions are still official, and a number of them constitute important and widely used classes of preparations.

When olive oil and water are put into a suitable container and shaken vigorously, a very temporary emulsion is formed. This is due to the fact that both the oil and the water are shattered into fine globules. These readily coalesce when the shaking has been discontinued, and the two liquids separate into their respective layers. The refusal of the liquids to remain dispersed is chiefly due to the fact that the surface tension of each of the liquids is great enough to pull the globules back together. Before either of these liquids can be made to remain dispersed in globules of microscopic sizes, some agent has to be used that will overcome their surface tension. In the case of pharmaceutical emulsions, acacia, gelatin and tragacanth function in this capacity rather well. If acacia is mixed with the oil or, in some cases, with the water before the water and oil are shaken, the oil will remain dispersed and a more or less permanent emulsion results. In the case of cod-liver-oil emulsion there results what is known as an oil-in-water emulsion. That is, the oil is the **dispersed phase** and water, with the aid of the acacia, is the **dispersing medium.** The presence of the acacia in the water overcomes the surface tension of the latter so that it spreads out into an elastic thin film surrounding the finely dispersed oil globules in such a way that they cannot coalesce. These finely dispersed globules of oil float in the medium, with a thin film of hydrated acacia molecules between them. If by chance the oil globules are able to break the film, they gradually unite into larger and larger globules and finally separate out as free oil. When this happens we say that the emulsion has broken or cracked. Fixed oils and most volatile oils are lighter than water and, of course, float upon it. Emulsified oil globules have a tendency to rise to the top; this results in **creaming,** like the cream that forms in a bottle of milk. Such cream layers may be made to rediffuse by shaking. Creaming, therefore, does not crack the emulsion as does separation of the free oil.

Perhaps the point should be made that, all other things being equal, the **finer** the oil globules, the more **permanent** the emulsion. In making emulsions, therefore, it should be the aim of the

operator to get the oil finely divided by a very rapid movement of the pestle, in the case of the mortar method, and by almost violent shaking in the case of the bottle method. Machines make better emulsions than one is able to make by hand only because they do a better job of shattering the oil into uniformly finer particles.

Colloidal Nature of Emulsifying Agents.—It has been observed that emulsifying agents are usually colloidal substances. This is true in the case of acacia, gelatin, tragacanth, chondrus, agar, soaps, clays, and similar products used as emulsifying agents. In water they form colloidal solutions and are termed hydrophilic, *i.e.*, water-loving, colloids. In the preceding discussion, mention was made of the fact that the acacia solution forms a film around each oil globule, thus preventing coalescence of the latter. This is explained by the fact that the acacia particles, or those of other hydrophilic colloids, gather at the oil-liquid interface and form effective barriers against the coalescence of the oil globules.

Perhaps it should be stated that the molecules at the surfaces of liquids are differently oriented with respect to the inner molecules of the same liquid and to the air or other substance in contact with them. One may put a drop of oil upon water and not see much happen although it is not hard to imagine that the molecules at the surfaces of contact are perturbed and are constantly rearranging themselves. Meanwhile, the insoluble oil rests upon the water as a large, round globule slightly depressed at the surface of contact. A similar drop of oil upon the surface of a solution of soap or acacia or an alkaline solution disappears into the liquid or becomes, at least, much smaller. The presence of these substances in the water has caused partial emulsification of the oil even without agitation. The soap and acacia particles gather at the surface of contact between the two immiscible liquids, oil and water, and, being hydrophilic colloids, cause the surface tension of the water to decrease. This makes the water more elastic and capable of enveloping the oil, especially if the latter is shattered into small globules by some means. These colloids are therefore emulsifying agents. If the oil, water, and emulsifier are subjected to the proper degree of agitation, a good emulsion will be formed.

It may take some imagination on the part of the beginner to accept this explanation of the formation of emulsions. However, there seems to be sufficient experimental evidence to make it seem plausible in view of the fact that we have no better way of explaining the problem.

The lowering of the surface tension of water by such hydrophilic colloids as acacia and soap serves well in making the oil-in-water type of emulsions. To form the water-in-oil type of emulsion, the emulsifying agent must lower the surface tension of the oil instead of the water as indicated in the discussion above. In this case, the water becomes dispersed in the oil. A good example of such an emulsion is that of Lime Liniment. The calcium hydroxide of the limewater reacts with the free fatty acids of the linseed oil to form a calcium soap, which upon agitation emulsifies the remainder of the water, forming Linimentum Calcis N.F. VII. Divalent bases, such as calcium hydroxide in limewater, and trivalent bases produce water-in-oil emulsions. Soaps of the univalent bases produce oil-in-water emulsions. As emulsifying agents, the soaps of divalent and trivalent bases behave in the same way as the soaps of univalent bases; *i.e.*, they arrange themselves at the interface between the two immiscible liquids, thus serving as emulsifying agents.

Many theories on the subject of emulsification have been advanced within the present century, but it cannot be said that any one explains all conditions that obtain in a system so complicated as an emulsion. The theories most commonly known are (1) the viscosity theory, (2) the hydration theory, (3) the surface-tension theory, (4) the adsorptive-film theory, and (5) Langmuir's theory of molecular orientation. These theories have been fully discussed in chemical and industrial literature of the past few decades, but most of the discussion is too technical to be reviewed here. Detailed information may be found in works dealing with this subject.

The Preparation of Emulsions.—There was a time when the making of emulsions was a bugbear to the average pharmacist because he was aware that success or failure depended on following the correct procedure. Emulsions, however, are easy to prepare even though a certain amount of care and skill may be necessary in order to obtain a good product. While pharmacists

are not often called upon to make emulsions, they need to know about them. Emulsions of fixed oils of various kinds include some important medicinals.

There are two methods of making fixed-oil emulsions, namely, the continental and the English. The continental method is the most commonly used procedure and one especially adapted to the beginner. To prepare 100 cc. of Emulsion of Cod Liver Oil one should proceed as follows: Mix carefully in a mortar 12.5 Gm. of powdered acacia with 50 cc. of the oil. Next add 25 cc. of water to this mixture, and triturate rapidly until a primary emulsion is formed. This should take place within a short time and is indicated by a distinct increase in viscosity and a sharp clicking sound upon trituration. Next add the flavoring and sweetening agents, transfer the emulsion to a graduated container, and make up to quantity by adding water, using it in small portions to rinse out the mortar.

Success with this method depends largely on the speed of the trituration after the water has been added to the mixture of oil and acacia. It is essential for the mortar and all necessary vessels to be clean and dry and also for the acacia to be thoroughly mixed with the oil prior to adding the water to make the primary emulsion.

The proportions of acacia, water, and oil in making primary emulsions are in the ratio of 1, 2, and 4, respectively, as illustrated by the continental method for preparing Emulsion of Cod Liver Oil. These are considered to be favorable proportions and may be varied somewhat, but not without limit. An increased amount of acacia would result in thicker emulsions. A lesser amount would result in thinner emulsions, which, if carried to extremes, would yield emulsions so thin that the oil would readily separate. On the other hand, an emulsion containing only 10 per cent oil would require an increased amount of the emulsifying agent to stabilize it. Fixed-oil emulsions contain 25 to 65 per cent oil, the average being about 50 per cent.

The English method requires the same ingredients, but the proportions and the procedure are different. To make Emulsion of Cod Liver Oil by this method, prepare a mucilage of the acacia and water in the proportion of about 15 Gm. of gum to

30 cc. of solvent. To this mucilage, in a mortar, add the oil in small portions, triturating after each addition until emulsified. A total of 30 cc. of oil should be used for the amounts of water and acacia indicated above. The formula is comprised of acacia 1, water 2, oil 2, which varies from that of the continental method. The English method is used in making mayonnaise; in this case, egg yolk serves as the emulsifier, and the oil is added a little at a time and emulsified after each addition by trituration or whipping in the usual way.

The above methods may be carried out by agitation in a bottle or by using egg beaters or mechanical emulsifiers of various kinds. All these ways of making emulsions not only are adaptable for fixed oils but may be used to emulsify liquid oleoresins such as copaiba and solids such as camphor, salol, menthol, resins, and waxes. The latter should be dissolved in oils before being emulsified. If any quantity of waxes is to be emulsified, this may be done by melting them before emulsification. Warm water and a warm mortar, also, would be necessary for this operation.

Emulsions of volatile oils and other volatile liquids, especially volatile oils, may be made by the continental and the English method; but inasmuch as they are thin liquids and at the same time quite volatile, it is perhaps wise to make them in a bottle, with brisk agitation. A proportionately larger amount of emulsifying agent may be needed for volatile liquids than for fixed oils. Emulsion of Oil of Turpentine is a good example of this, where 5 Gm. of acacia is required to emulsify 15 cc. of the rectified oil for each 100 cc. of the finished emulsion. However, stable emulsions may be prepared with much smaller proportions of emulsifying agent to volatile oils than is indicated in the above formula. The stability of volatile-oil emulsions may be increased by mixing them with about an equal amount of a fixed oil prior to emulsification. As a rule, volatile-oil emulsions show creaming more readily than fixed-oil emulsions. However, the cream layers are usually easily diffused upon shaking.

Emulsifying Agents.—Reference has been made to the fact that acacia is the emulsifying agent of first importance in pharmaceutical emulsions. This is largely true so far as the official emulsions are concerned, but there are several other substances

that are satisfactory emulsifiers. A few of these will be briefly described.

Next to acacia, **tragacanth** is perhaps the most popular emulsifying agent used in pharmacy. Since it is largely insoluble, only about one-fourth to one-tenth as much of it, as compared with acacia, is needed as an emulsifier. The viscid, gel-like nature of the mucilage gives it the properties of emulsifying oil globules and retarding their coalescence. Emulsions made with tragacanth are therefore more viscous than those made with acacia. For this reason, it has been used in emulsifying thin liquids.

Mucilage of **Irish moss** is used in the large-scale manufacture of emulsions and sometimes in small-scale production. In favor of its use are the facts that it is cheap, yields a mucilage with high viscosity, and produces white emulsions. In the form of a mucilage it spoils easily, and so preservatives of some kind, sodium benzoate, for example, are necessary when it is used. Acacia, tragacanth, gelatin, agar, and substances of like nature in the form of mucilages and dilute solutions have a tendency to spoil, and preservatives are always necessary.

Agar is considered a good emulsifying agent for heavy liquids. It is so sparingly soluble that not more than 1 to 1.5 Gm. per 100 cc. of emulsion can be used. Lesser amounts are often used with acacia, the latter being necessary to give stability and whiteness to the emulsion.

Gelatin solution is sometimes used to emulsify liquid petrolatum. The emulsifying power of gelatin solution is increased by dissolving an amount of potassium carbonate in it equal to, or somewhat greater than, the amount of gelatin used. Emulsions of this kind are said to have some use in veterinary practice.

Yolk of egg is a valuable emulsifying agent. It is about the only agent that can be used when acids or large proportions of alcoholic solutions are to be added. Mayonnaise, which is so widely used, is made sour, or tart, to the taste by the use of vinegar or lemon juice. This is possible because egg yolk is the emulsifier. Glycerite of egg yolk is reputed to be a good emulsifying agent, especially for chloroform, creosote, and resinous tinctures.

Other substances that have emulsifying properties but a limited use in pharmacy are condensed milk, casein, pancreatin,

dextrin, extract of malt, honey, tincture of quillaja, tincture of senega, soaps, and certain insoluble substances such as milk of magnesia, lampblack, precipitated calcium carbonate, bentonite, talc, fuller's earth, and silica gel. Certain of these substances have more extensive uses in the preparation of commercial spraying liquids.

Of the newer emulsifying agents, triethanolamine and its esters are well known. Commercial triethanolamine, which has certain disadvantages as an emulsifying agent, is considered to be a mixture of bases, principally trihydroxytriethylamine $[(CH_2CH_2 \cdot OH)_3 \equiv N]$. It reacts with the fatty acids of oils and fats, forming soaplike products that lower the surface tension of water. The oil present is readily emulsified by agitation in the usual manner. These soaps are used widely in the toiletry industry.

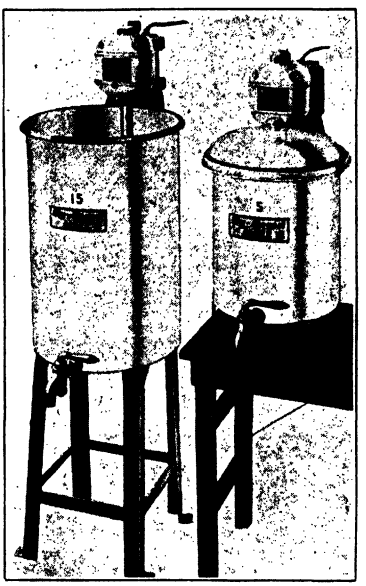

FIG. 94.—Alsop Hy-Speed electric mixer.

Certain of the higher alcohols, among them cholesterol and cetyl alcohol, are useful for water-in-oil emulsions. Sulfonated oils and certain sulfates of the higher fatty acids are coming into use in the making of ointments and lotions for external use.

Emulsion Machines.—Emulsifying machines of the simpler types have been known in pharmacy for a long time. The Phenix emulsifier was an early example of the enclosed egg beater of the hand-driven type. Emulsifiers of this kind made it possible to produce emulsions in gallon quantities.

The variable-speed emulsifier operates on the same principle except that it is motor driven and the speed can be varied. The capacity of this machine ranges from 5 to 50 gal.

Kitchen and soda-fountain electric mixers of various kinds have been used for making quantities of less than one gallon.

Colloid mills of various types serve as emulsifiers in some instances. They subject the emulsion mixture to a tremendous shearing action, which causes the oil globules to be finely dispersed.

Milk and other emulsions are often homogenized. Homogenizers are made to operate at high pressures, 1,000 to perhaps

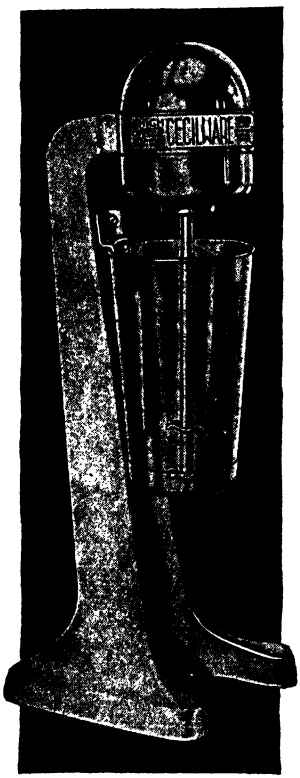

FIG. 95.—Mechanical emulsifier.

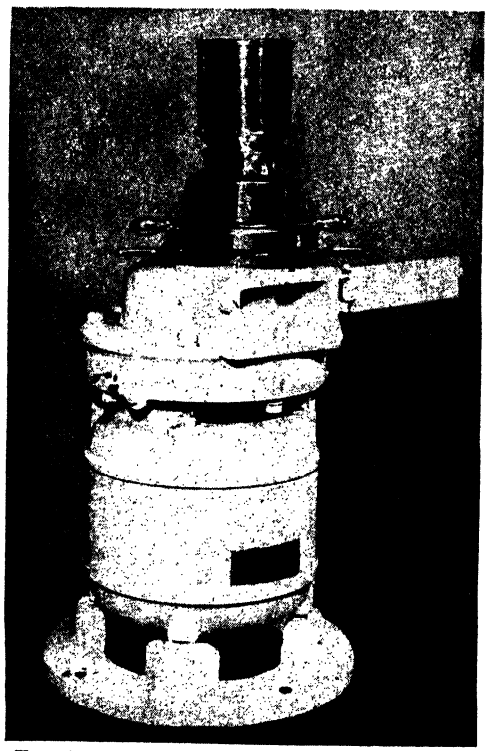

FIG. 96.—Laboratory model of a triple-action colloid mill. (*Courtesy of C. O. Bartlett & Snow Company.*)

5,000 lb. per sq. in. The emulsion mixture is forced through a fine opening under great pressure against a valve head. The impact causes the globules of the emulsion to be shattered into innumerable smaller ones. Microscopic examination of a handmade emulsion will as a rule show the oil globules to be quite large on the whole and lacking in uniformity as to size. Examination of the same emulsion after it has been

homogenized shows that the oil globules not only have been greatly reduced in size but are quite uniform. Homogenized emulsions are much smoother and show creaming at a much slower rate than handmade emulsions. Emulsions may be recirculated through the machine, increasingly finer dispersion being the result.

One point of comparison between homogenizers and the stirring type of machines is that the former do not beat air into the emulsion. The presence of an undue amount of air in emulsions is sometimes a source of trouble, even hastening spoiling when certain emulsifiers are used.

Not many pharmacists can afford to have a power homogenizer as a part of their equipment, but there is a small hand homogenizer on the market that is very reasonable in price.

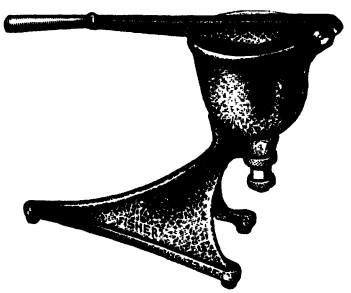

FIG. 97.—Hand homogenizer.

The Official Emulsions.—There are three emulsions in the twelfth revision of the Pharmacopoeia and four in the National Formulary VII. Of this number, four are fixed-oil emulsions, two are emulsions of liquid petrolatum, and one is a volatile-oil emulsion. The emulsifying agents used in the official emulsions are acacia in five, tragacanth and extract of malt in one, and glycerite of egg yolk in one. Nothing is added, in the case of Emulsion of Asafetida U.S.P. XI, except water. Asafetida is a dried gum resin. When it is mixed with water, the gum dissolves and serves as the emulsifying agent for the insoluble resins present.

The official emulsions have been thought of as extemporaneous preparations. However, permission is now given to vary the excipient and the method of making of certain of these emulsions so that it is possible for manufacturers to make official emulsions to be packaged and distributed in the usual way, provided that such emulsions are similar in viscosity and appearance to those made strictly by official methods. The use of a mechanical mixer is especially recommended for making Emulsion of Liquid Petrolatum with Phenolphthalein. The presence of agar

makes it difficult to get a very satisfactory product by hand manipulation. In making Emulsion of Cod Liver Oil, permission is given to replace the methyl salicylate with other desirable flavoring agents in an amount not to exceed 1 per cent. If the emulsion is to be prepared as a stock item, 7 per cent by volume of alcohol, replacing an equal volume of water, is recommended.

Heavy liquid petrolatum is advised in the formula for Emulsion of Liquid Petrolatum. Mineral-oil emulsions have become a popular form of medicine in recent years. The official formula may be accepted as representative of these preparations.

The extract of malt in the Emulsion of Cod Liver Oil with Malt is added essentially to improve the taste. However, malt has food value and because of its viscous nature aids in stabilizing the emulsion. If Emulsion of Cod Liver Oil with Egg is to be kept for any length of time, some preservative in addition to the 8 to 9 per cent of alcohol present in the formula should be added because the egg spoils easily.

MISCELLANEOUS NOTES CONCERNING EMULSIONS

Color.—Most emulsions are white, a few are yellowish, and all are opaque. Transparent emulsions are possible when the refractive powers of the immiscible liquids equalize each other. Substances may be added to one liquid or the other to bring this condition about.

Ingredients.—There are three ingredients essential to every emulsion, two immiscible liquids or substances and the emulsifying agent. This holds also for the so-called "solid" emulsions such as butter, cold creams, hydrous lanolin, and axle grease. Of these constituents, one seems to be as important as another. Nature has caused incompatible substances, such as oil and water in milk, to exist harmoniously together. By the exercise of knowledge and skill man is able to make a great variety of emulsions for many uses in medicine, technology, and industry.

Emulsifying Agents.—The emulsifying agents are usually gums, mucilages, albumens, proteins in solution, or suspensions in favorable concentrations. Certain of these substances form very viscid liquids or gels closely resembling mucilage of tragacanth. Emulsification with such agents is a more difficult procedure, but the product is perhaps a little more permanent.

Emulsifiers of this type spoil readily; so preservatives of some kind, such as alcohol (8 to 12 per cent), benzoic acid, and sodium benzoate are frequently added, especially if the emulsion is to be kept for some time.

The Agitation.—Brisk agitation is needed to make emulsions. If the emulsion does not form after a few moments of rapid trituration, shaking, or stirring, there is little hope of success by continued effort. Instead, a new start should be made and the process repeated.

It should be borne in mind that in making emulsions the briskness of the agitation is the essential feature in the procedure. One might stir or shake an emulsion mixture in a leisurely manner all day without causing it to emulsify. Furthermore, when the emulsion has once formed continued agitation is of no value. In fact, if continued too long, it might cause the emulsion to break owing to the coagulation of oil globules.

Flavors.—Flavors are added to emulsions to improve the taste. The usual pungent flavoring oils are not so pleasant and satisfactory as the softer flavors like chocolate syrup, coffee syrup, vanilla extract, and extract of licorice. The oils of anise and cardamom have been recommended, but oils like cinnamon, wintergreen, and caraway seem to accentuate the fishy taste of cod-liver oil.

Just when the flavoring agent should be added to the emulsion to be most effective is a moot question. Some authorities advise adding the flavor with the oil prior to emulsification, especially in the case of cod-liver oil. Others argue that better results are obtained by adding the flavors to the primary emulsion. It has been argued that the best results are obtained by adding the flavor in part to the oil to be emulsified and in part to the primary emulsion.

Sweetening agents of some kind are needed with the flavors for emulsions. Syrup or saccharine solutions are those most frequently used. Undissolved sugar should not be used, nor should an emulsion be too sweet. In the case of cod-liver-oil emulsions, a little salt may improve the taste, but strong electrolytes are incompatible with emulsions.

Breaking Emulsions.—Emulsions are reasonably stable but may be easily split or broken by chemical and physical means.

They may be broken also by exposure to extremes of heat or cold, especially freezing temperatures. The addition of strong electrolytes, in the form of either salts or solutions, and alcohol in high concentrations tends to break emulsions. These agents may affect the emulsifying agents or disturb the water phase in such a way as to destroy the emulsion system. Continued agitation has been known to break emulsions.

Distinguishing Types of Emulsion.—An oil-in-water emulsion may be diluted with water, within certain limits, without danger of breaking. The water-in-oil emulsion, however, cannot be diluted in any such fashion.

An oil-in-water emulsion will conduct an electric current, while the water-in-oil emulsion will not. This is due to the fact that the water in the oil-in-water type of emulsion is the external phase and, except in special cases, contains electrolytes sufficient for the passage of a measurable current through it.

The use of oil-soluble Sudan III dye has been recommended as a way of determining the type of emulsion. It should be added to the oil before dispersion. The dispersed globules, upon examination under the microscope, should show color. Water-soluble dyes, such as methylene blue, have been used in a like manner. However, this method is not wholly satisfactory.

STUDY QUESTIONS

1. Give the meaning of the word *emulsion*.
2. Give the older definition for emulsions, and compare it with the modern definition.
3. Explain the emulsion phases.
4. Give examples of (*a*) natural emulsions, (*b*) artificial emulsions.
5. Explain how it is possible to cause immiscible liquids to exist homogeneously together.
6. Explain (*a*) primary emulsion, (*b*) creaming, and (*c*) breaking as applied to emulsions.
7. Discuss the chemical nature of the commonly used emulsifying agents.
8. Explain the terms *oil-in-water* and *water-in-oil emulsions*.
9. Explain and distinguish between the continental and English methods of making emulsions.
10. How do volatile oils and fixed oils differ in respect to emulsifying problems?

11. Why should acacia not be used as an emulsifying agent in making mayonnaise?

12. How does triethanolamine function as an emulsifying agent?

13. Explain the types of emulsifying machine.

14. Discuss the problem of sweetening and flavoring emulsions.

15. How may one distinguish between emulsion types?

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CHAPTER XV

EXTRACTION

The process of extraction is made use of in pharmacy to obtain the desirable soluble constituents of both vegetable and animal drugs. It is also used to purify the desirable insoluble portions of certain drugs. It is widely used not only in the pharmaceutical industry but in many other industries as well.

The process is one of partial solution; complete solution of the drug under treatment is not expected. In pharmacy the undissolved residue of the drug that remains after being subjected to extraction is called the **marc.** The solvent used is commonly referred to as the **menstruum.** These features help to distinguish the process from one of complete solution.

The Ebers Papyrus (1552 B.C.) indicates that the process of extraction was known to the Egyptians and that water was the common solvent. During the Greek period it seems that wine became a solvent for the extraction of drugs. Galen (A.D. 130–200) is credited with having introduced the use of vinegar as a solvent. Several centuries later the alchemists prepared alcohol from wine and used it as a menstruum for making tinctures.

While certain extraction procedures require the use of such organic solvents as ether, chloroform, or acetone, water or alcohol alone or hydroalcoholic solutions of varying proportions are the most commonly used menstruums. The choice of solvent to be used in an extraction experiment is determined largely by the nature of the product or products to be extracted. Therefore to understand extraction requires considerable knowledge about the drug itself and the solubility of its desirable constituents. The product of the extraction process is often referred to as the *extractive.*

It is not at all easy and it is not often practicable to extract drugs to complete exhaustion. The cellular nature of drugs virtually precludes this. No matter how carefully one carries

out the extraction, the capillary nature of the cellular structure of drugs will retain certain amounts of the liquid even though the whole is subjected to expression. The liquid so retained contains a certain proportion of the soluble constituents of the drug. This leads to an important principle that should always be followed in extraction processes: A drug is much more effectively extracted by repeated applications of small portions of the menstruum than by one or two applications of much larger volumes.

Other conditions being the same, powdered barks and leaves are more easily extracted than seeds and root drugs. In the former the cellular structure is more open and woody and the cell content is freer of troublesome gums, mucilages, and starches than in the latter group. Tannin is a plant constituent that is widely distributed in nature and that is found in large amounts in bark and leaf drugs. It is soluble in most of the solvents, is to be found in the extractive preparations, and is often a source of incompatibilities.

The process of extraction has extensive pharmaceutical use in the preparation of infusions, decoctions, tinctures, fluidextracts, resins, oleoresins, and vinegars. These extractive preparations are made by the application of one or more of the extraction processes, namely, maceration, expression, percolation, digestion, infusion, and decoction.

In carrying out an extraction process it is necessary to give attention to the condition of the drug. Some drugs may be easily extracted in the form of coarse powders. Others need to be finely powdered in order to ensure proper extraction. In any case the drug particles should be fairly uniform in size. In certain cases, some form of agitation ensures a more thorough extraction of the drug. The extraction process has made it possible to obtain the active medicinal agents of many plants such as quinine from cinchona, strychnine from nux vomica, and morphine from opium, all of which are highly purified chemicals of inestimable therapeutic value.

Maceration.—The process of maceration is one of soaking the drug in the menstruum prior to expression or percolation. It is usually carried on at room temperature and extends over a period of time from a few moments to several days. At the

expiration of the period the liquid is separated from the drug by decantation, percolation, filtration, or straining, sometimes followed by expression. Maceration finds application in the making of tinctures from drugs that do not percolate well. These include such balsamic drugs as tolu and benzoin. With alcohol or other volatile menstruums, maceration should be carried on in closed containers. Fruit jars of the proper size are good for this purpose. Even so, the process is not a very efficient one because it is difficult to exhaust the drug by this method. However, a number of the tinctures of the twelfth revision of the Pharmacopoeia and the seventh edition of the National Formulary are made by the maceration process.

The process of **digestion** is merely a modification of the maceration procedure and differs from the latter only in that it is carried on at temperatures somewhat higher than room temperature.

Infusion.—The process of infusion is usually that of the solvent action of boiling water on drugs. Cold water is used in certain instances. The drug particles should be uniform in size, usually in a coarse state. The drug may be suspended in the hot water in a porous bag of some kind. However, the usual procedure is to put it in a suitable vessel, usually of porcelain or glass, and to pour boiling water on it. The drug is allowed to soak in the water until the latter is cool or perhaps for a specified time, 30 min. in the case of infusion of digitalis. After the proper period of soaking has elapsed, the drug, if suspended in a bag, may be removed. If in the water it may be removed by straining or filtering. In either case, the residue is usually expressed.

The making of tea is a good example of the infusion process. The desirable constituents are water-soluble and often volatile and aromatic.

Infusions are extemporaneous preparations and are little used in this country. None are official in the twelfth revision of the Pharmacopoeia. Three are official in the seventh edition of the National Formulary. The general formula of the Pharmacopoeia for making infusions states that 50 Gm. of the drug should be used for each 1,000 cc. of the finished product.

Decoction.—In preparing decoctions, the drug, in a coarse state of division, is put into cold water and the whole boiled

for a stated length of time, fifteen minutes or longer. This is done in a covered container of suitable capacity, and the mixture strained after cooling. The preparation of coffee by boiling is a good example of the decoction process. The residue, after straining, may be washed with additional water, expressed, and made up to the proper volume.

Decoctions, like infusions, should be freshly prepared, for water extractives and mucilaginous and albuminous constituents from the drug, along with those which are more desirable, are good media for the growth of fungi, molds, and bacteria. For this reason decoctions may show deterioration within a few hours. The use of preservatives for such preparations is usually avoided although the small amount of alcohol used in making Infusion of Digitalis acts as a preservative.

Most of the so-called "extractive" liquid preparations show the formation of a sediment upon standing. Infusions and decoctions are perhaps the worst offenders in this respect. The longer they stand, the worse they appear especially if fungi and molds develop.

Infusions and decoctions are a much more acceptable form of medicine in the countries of Europe and Asia than in America. Much attention is given, in these countries, to the use of the proper vessels. Infusion jars, usually of porcelain, are well known. These serve in the same way as do teapots for making tea. Decoctions are often prepared in earthenware casseroles. Enameled ironware vessels may be used for the same purpose.

Lixiviation.—An old term used to describe a crude form of extraction is **lixiviation.** This is often referred to as *leaching.* The process has application in extracting inorganic material, usually present in small proportions. Extraction, as usually carried on in pharmacy, is chiefly for the purpose of obtaining soluble organic material. In the early days in this country it was a common practice to collect the wood ashes from stoves, put them into barrels or similar containers, and pour water over them. In passing down through the ashes the water dissolved out the soluble alkali carbonates. With proper attention to the process the drip from these barrels was strongly alkaline and served as a source of lye to the early settlers, who used it in making soap and for other purposes.

This form of percolation is used in the arts and for extracting marine plants but is not used extensively in pharmaceutical practice.

Percolation. *Theory and Problems.*—As a process of extraction, percolation is not always applicable, but it is perhaps the most widely used of all the methods, especially in pharmaceutical practice. By the percolation process it is possible to extract a drug completely with the minimum amount of menstruum and with no need of filtering the percolate as this is automatically cared for in the procedure.

Percolation may be defined as a process by which drugs are extracted by allowing a menstruum to pass through them in a suitable container called a **percolator.** The menstruum is usually allowed to flow by gravity downward through the drug, but it may be made to flow up through the drug by pressure. The principle of the percolation process was made use of long before it was applied to drug extraction, as was mentioned in connection with the leaching of wood ashes, a process that was known centuries before it was used to prepare medicinals. Percolation is included in all the modern pharmacopoeias.

The percolation procedure is a simple one. Yet when one tries to understand what occurs when a menstruum passes downward through a drug in a percolator, a number of complications present themselves. First, dried drugs are used. This means that the cell contents and the cellular structures are dry and shrunken and under such conditions do not respond to the solvent action of liquids and chemical substances as live tissues do. Second, drugs are subjected to percolation with a view to dissolving out certain of the valuable constituents. Since most of the solvents used for this purpose are not highly selective, many undesirable constituents are extracted along with the desirable ones.

There is more to a successful percolation experiment than merely pouring the menstruum upon the drug. First the drug needs to be properly prepared as to degree of fineness. It must be allowed to soak in the menstruum for a while before being subjected to percolation. This permits the dry drug to become moistened and to swell, which makes it possible for the men-

struum to permeate the softened and ruptured cellular structures. At the same time the dissolved constituents will diffuse out and be carried down as a part of the percolate. Successive additions of fresh menstruum to the drug cause a change in the concentration of the liquid residue within the marc. This in turn sets up further diffusion of the soluble cell constituents and causes more of them to be carried out into the percolate.

Since the principle of diffusion is at work in the percolation process, the menstruum should not be allowed to pass through the drug too rapidly. After the addition of a fresh quantity of the menstruum to the drug a period of maceration should follow before percolation is allowed to proceed. Some have suggested a period of 24 hr. This would not be necessary if the rate of flow of the percolate were carefully regulated. The rate of flow of percolation should be slow enough to guarantee the maximum degree of extraction.

Some drugs may be macerated quite well in the percolator. Others swell to such an extent that preliminary maceration should take place in a closed container. In small operations, fruit jars serve the purpose satisfactorily. After such a maceration period the damp drug may be transferred to the percolator, properly packed, and percolated in the usual manner. Husa[1] and his coworkers have given considerable attention to the problem of the permeation of cell walls by various solvents and to the influence of the structure of vegetable drugs on the extraction of their constituents. Their results indicate that water causes the greatest amount of swelling of plant tissues, that glycerin, while more slowly absorbed, causes swelling about equal to that of water, and that alcohol will cause some swelling. These workers conclude also that long periods of maceration are not necessary for complete swelling and extraction and that powders from No. 20 (coarse) to No. 80 (very fine) fineness have no particular influence on the efficiency of extraction.

History.—While the principle and the process of percolation have been understood and used as a crude method of extraction for a long time, only recently has it been used to extract drugs.

[1] W. J. Husa. *J. Am. Pharm. Assoc.* **23**, 891–901, 980–4, 1097–1103, 1187–96 (1934).

Couch[1] says that to two Frenchmen, Robiquet and Boutron, belongs the credit for introducing percolation as a method in organic chemistry but that the Boullays, father and son, should be given credit for establishing it as a pharmaceutical process about 1835. The Boullays were skillful pharmacists and by experimentation showed that percolation is superior to the old process of maceration. These investigators insisted that this method of displacement, as they called it, had a great future and should revolutionize pharmaceutical practice. Other French workers did much to confirm the observations of the Boullays and to establish percolation as an extraction process in pharmacy.

French pharmacists are therefore considered to have established percolation as a pharmaceutical procedure. To American pharmacists belongs the credit for developing and applying it extensively in pharmacy. A. Duhammel in 1838 was the first American to write about it, and E. Durand of Philadelphia was perhaps the first to make use of it. Other American pharmacists who have contributed much to the knowledge and use of percolation are Procter, Grahame, Squibb, Diehl, Lloyd, Oldberg, Scoville, and Husa. It is still a subject of considerable study and investigation.

Percolators.—Pharmacists recognize the percolator as a special piece of equipment of well-established conformation and usually made of glass. Percolators also are often made of metal, which is frequently lined with glass. Large percolators have been made of wood.

There are three types of shape, namely, conical, Oldberg, and plain. A funnel is a good example of a **conical** percolator. As a matter of fact, funnels have been used at times as percolators and for certain extractions serve rather well. A funnel with its flaring sides allows drugs to swell without packing too tightly.

The **Oldberg,** or narrow, percolator is almost cylindrical in shape. For this reason the drug column is much longer as compared with its width than in plain or conical percolators. This should result in more efficient extraction of the drug per unit volume of the menstruum. The plain percolator is less conical in shape than a funnel but more so than the

[1] J. F. Couch. "Early History of Percolation," *Am. J. Pharm.* **91,** 18–24 (1919).

Oldberg percolator. It is referred to as the **ordinary** type of percolator and serves for most of the simple percolation exercises in pharmacy. These percolators are shown in Fig. 98.

There are practical variations of the three types of percolator in use. Long, narrow, cylindrical percolators have had some use in recent years in an experimental way. They permit a much longer drug column as compared with the diameter than ordinary percolators. Some are covered and equipped with a stopcock at the bottom so as to minimize evaporation of the

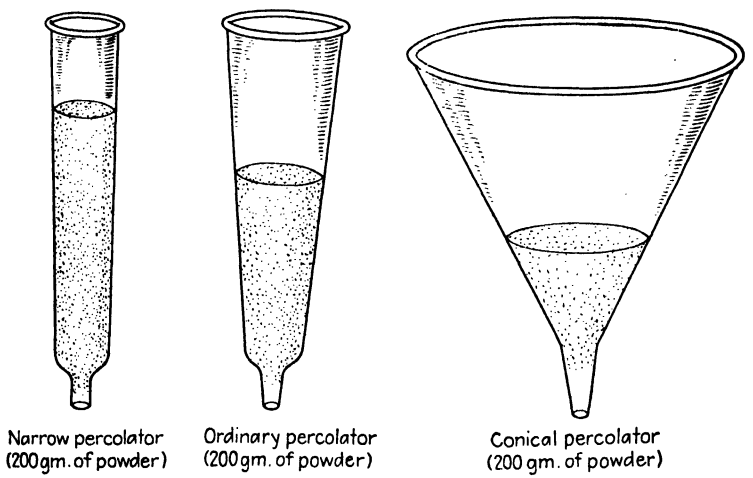

FIG. 98.—Percolators.

menstruum and regulate the flow of the percolate. Percolators of very large sizes are often seen in industry. These are usually made of metal and are sometimes porcelain- or glass-lined. Some are jacketed so that extractions may be made at increased temperatures.

Continuous Extraction.—The Soxhlet extractor permits continuous extraction to proceed for several hours, using a minimum of solvent. It is useful in extracting small amounts of certain ingredients such as fats, oils, oleoresins, and resins from drugs. It is dependent on the use of heat to volatilize the solvent, which in turn is condensed in such a manner as to drop upon the drug contained in a paper thimble. When a certain amount of the charged menstruum has accumulated, it siphons over

into the receiving flask and the menstruum is volatilized and starts on its round again. In this way, small amounts of menstruum are made to accomplish extraction over and over. This is a very useful process in certain assay determinations and in research (see Chap. XI).

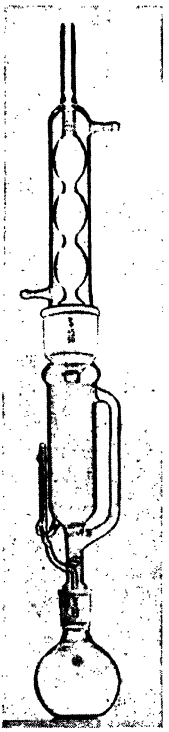

FIG. 99.—Soxhlet extractor.

The Lloyd extractor and concentrator makes use of the principle of continuous extraction. It is valuable equipment, especially for research and small-scale extractions. This extractor is an invention of J. U. Lloyd of Cincinnati, one of America's most illustrious pharmacists (Fig. 100).

Diacolation.—The process of diacolation was devised by Breddin, a German apothecary, in 1930.[1] The apparatus consists of a series of cylindrical percolators connected to each other. The menstruum is forced through the percolators by means of air pressure. It is rather troublesome to charge such equipment, but it is possible to get good extraction with a minimum amount of menstruum. The following workers have experimented with this method and report favorable results: Gstirner[2] and Keller[3] in Germany; and Husa and Huyck,[4] and LeFevre and Lee,[5] in America. The Upjohn Company, Kalamazoo, Mich., has recently installed several batteries of large percolators that operate upon this principle. This was done following an extended study of the process by W. F. Enz (Fig. 101).

Pressure percolation is based on the theory that if 1000 Gm. of drug is packed firmly in a sufficiently long column, extraction of the drug is assured by the collection of 1000 cc. of percolate.

[1] H. BREDDIN. *Pharm. Ztg.* **79**, 148 (1934).

[2] F. GSTIRNER. *Pharm. Ztg.* **79**, 310–2 (1934); *Chem. Abstracts* **28**, 3838 (1934); *Apoth. Ztg. Deut. Apotheke* **2**, 742–4 (1934); *Chem. Abstracts* **29**, 6700 (1935).

[3] F. KELLER. *Apoth. Ztg.* 49 **2**, 592 (1934); *Chem. Abstracts* **28**, 3835 (1934).

[4] W. J. HUSA and C. L. HUYCK. *J. Am. Pharm. Assoc.* **27**, 211–7, 280–95 (1938).

[5] H. F. LEFEVRE and C. O. LEE. *J. Am. Pharm. Assoc.* **29**, 233–6 (1940).

may become packed so tightly that the menstruum will not go through it. When this happens, the wisest thing is to decant the excess menstruum, transfer the wet drug to a suitable dish, and allow it to dry sufficiently for regranulation and repacking. Unless there is too much resin in the drug, it should percolate satisfactorily after such a treatment.

Most percolators are finished with a ground-glass upper edge. This makes it possible to close them tightly, during the maceration period, with a glass plate after the ground surface has been given a thin coat of petrolatum or glycerin. An airtight system is thus produced, and air must be admitted at the top of the percolator when the drug is ready for percolation.

After the percolation has started, to prevent it from drying out the drug should be kept covered with a layer of the menstruum. When the menstruum disappears from the surface, not only does the drug dry out but air gets into the capillary spaces and extraction is greatly retarded. Moistening the drug before packing not only causes it to swell and soften but allows occluded air to escape. If drugs are put into percolators in the dry condition, the finer particles trickle down toward the bottom of the percolator. Then, when the first menstruum is added from the top more of the finer particles are washed down and the lower end of the percolator is apt to become congested, all of which interferes with extraction.

The Rate of Flow.—Of the many factors influencing the success of percolation, one of the most important is the rate of flow of the percolate. If the rate is too rapid, the drug is not exhausted with the amount of menstruum allotted to the experiment. If too slow, much valuable time may be wasted and too great loss of the menstruum by evaporation may take place. The twelfth revision of the Pharmacopoeia indicates three rates of flow for fluidextract percolates, namely, "slowly," "a moderate rate" and "rapidly." The amounts of percolates to be collected for each rate are, respectively, not exceeding 1 cc. per min., 1 to 3 cc. per min, and 3 to 5 cc. per min. These rates of flow are not rigid but do serve as guides to the inexperienced. In the manufacture of tinctures in which the ratio of menstruum to drug is much larger, the rate of percolation can be much faster. In any case, the rate of flow should be designed so as

to extract the medicinal constituents of the drug with a minimum of the menstruum and within a reasonable length of time. This is especially so when concentrated percolates are sought.

Degree of Fineness of the Drug.—The degree of fineness of the drug under treatment is important. This in turn is dependent on the nature of the drug. For example, it is impossible to percolate squill in a finely powdered condition. However, cinchona, in a fine powder, is easily extracted. Finely powdered drugs are more easily extracted with strongly alcoholic or ethereal menstruums than with hydroalcoholic solvents. On the other hand, certain of the coarser powders are more readily extracted with hydroalcoholic and aqueous menstruums.

Exhaustion of the Drug.—The object of percolation and other extraction processes is to exhaust the drug of its important medicinal constituents. The simplest way to judge this is by the color, odor, and taste of the percolate. Almost all percolates from vegetable drugs show color. A colorless percolate indicates that the drug is exhausted at least with respect to color. The aromatic drugs impart odors to their percolates in about the same way; and the bitter-tasting drugs, such as cascara sagrada and quassia, gradually lose their bitterness upon being percolated.

In the case of those drugs which yield alkaloids such as nux vomica and cinchona, it is possible to subject a few drops of the percolates to chemical tests to detect the presence or absence of alkaloids. Resinous principles are easy to detect. This is done by adding a few drops of the percolate to water. Resinous substances in alcoholic solution usually show a white, cloudy precipitate when added to water. There are other tests that could be mentioned, but these are sufficient to indicate that there are many ways to judge the degree to which a drug has been exhausted by percolation.

When a quantity of drug has been exhausted, a certain amount of the menstruum always remains behind in the marc. For the large-scale manufacturer, the loss of large amounts of alcohol is something to be avoided. Under such conditions, the marc is usually expressed, centrifuged, or subjected to distillation for purposes of recovering the alcoholic residues in the extracted drug.

Since most percolates are more or less alcoholic, they should be collected in receivers of such shapes as will minimize loss by

evaporation. Narrow-mouthed graduated bottles serve the purpose well. If graduated bottles are not available, it is not difficult to put temporary graduation marks on the bottles being used.

Repercolation.—Perhaps no one American pharmacist ever gave more thought and effort to the problems of percolation than Dr. E. R. Squibb. He sought ways to economize in the use of alcohol without sacrificing the quality of the finished product. As a result of extended studies, he devised the repercolation process, sometimes termed the *Squibb process.* He defined it as "the successive application of the same percolating menstruum to fresh portions of the substance to be percolated."

The process for making fluidextracts was carried out as follows: 1,000 Gm. of the drug was divided into five 200-Gm. portions. These were numbered 1, 2, 3, 4, and 5, respectively. Portion 1 was moistened, packed, and percolated in the usual way. The first 150 cc. of the percolate was set aside as a portion of the finished product. Percolation was continued, the percolate being collected in 200-cc. portions until the drug was exhausted, which meant that perhaps four or five portions were collected. These may be designated *a*, *b*, *c*, *d*, *e*, etc. A second 200-Gm. portion of the drug was then moistened with weak percolate *a* and packed and percolation continued, the weak percolates *b*, *c*, *d*, and *e* being used in succession. The first 200 cc. of this percolate was set aside as a portion of the finished fluidextract. The percolation was continued in the manner just described, fresh menstruum being used at the end if necessary. The third, fourth, and fifth portions of the crude drug were extracted in this manner. The five lots of reserved portions, totaling 950 cc., were then combined. In addition, there were four or five lots of weak percolates *a*, *b*, *c*, *d*, and *e* to be set aside for use in extracting the next lot of the same drug.

Naturally, a certain amount of the extractive material was retained in the weak percolates. Dr. Squibb was able to show that a weak solution of the constituents of a drug is a better solvent for the active principles of the crude drug than the plain fresh menstruum. This observation gave much support to the repercolation process. Process *C* of the Pharmacopoeia is similar to the Squibb process.

Most of the problems of percolation seem to center in the manufacture of fluidextracts, owing perhaps to the fact that they are the most difficult class of the extractives to prepare. The Pharmacopoeia and the National Formulary describe the processes by which fluidextracts are made. The student is referred to these books for the details for making not only fluidextracts, but also extracts, tinctures, resins, oleoresins, and other preparations made by the process of extraction.

Much more detailed discussions of the extraction process may be found in the references at the end of this chapter.

STUDY QUESTIONS

1. Explain the term *partial solution.*
2. Explain the difference between solvent and menstruum.
3. Why are drugs more thoroughly extracted by repeated applications of small amounts of a menstruum than by one application of an equal amount?
4. Name several important pure chemicals obtained by extraction.
5. Why is the process of infusion unsuited for making decoctions, and vice versa?
6. In the process of percolation explain why so much attention is given to (*a*) proper size of drug powder, (*b*) maceration, (*c*) packing of the drug in the percolator, (*d*) rate of flow of the percolate.
7. What is meant by diffusion, and how does it apply to processes of extraction?
8. Explain some of the ways to determine whether or not a drug has been exhausted by percolation.
9. Explain (*a*) the pressure-percolation procedure, (*b*) the process of continuous extraction.
10. Explain the process of repercolation and its advantages, if any.

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CHAPTER XVI

PRECIPITATION, CRYSTALLIZATION, AND GRANULATION

Precipitation.—Precipitation is the process of separating one or more constituents of a clear liquid into a finely divided solid form. This is usually accomplished by mixing two clear solutions. If, when the solutions are mixed, the proper conditions of ionic equilibriums are set up, *i.e.*, if the right ions are present under the proper influences, certain pairs or groups of ions will unite to form molecules of compounds which are only slightly soluble in the liquid that produced them. The solid that is formed separates out and is called a **precipitate.** A precipitate, therefore, may be defined as a solid separating from a solution. The physical character of a precipitate is usually described by the terms *crystalline, granular, bulky, heavy, dense, flocculent, gelatinous,* or *amorphous.* Terms descriptive of color and quantity are also used.

The importance of precipitation to pharmacy cannot be overemphasized. It is intimately connected with the manufacture of medicines, their qualitative and quantitative analyses, their preservation, their incorporation into prescriptions, and their functioning as therapeutic agents in the body. Some of its applications to pharmacy are described below. As the student becomes more familiar with his profession, he will be able to extend the list appreciably.

The manufacture of medicines is greatly facilitated by the process of precipitation. Precipitated Chalk of the Pharmacopoeia is an example of a drug made by this method. A solution of calcium chloride is treated with a solution of sodium carbonate, which causes insoluble calcium carbonate to form and to separate out in a fine state of subdivision. The official bismuth salts are largely made by precipitation methods. It is obvious that only those compounds which are relatively

insoluble can be satisfactorily made by this procedure. There are times, however, when the insolubility of a compound becomes troublesome, so that in some manufacturing processes the pharmacist and pharmaceutical chemist have the problem of guarding against undesirable precipitation. Pharmaceutical manufacturing laboratories making Solution of Lead Subacetate N.F. VII must take precautions against the precipitation of the very insoluble lead carbonate in the finished product. Pharmacists making Solution of Iron and Ammonium Acetate N.F. VII must guard against the iron being subsequently precipitated as a basic ferric acetate.

Careful control of tendencies toward precipitation frequently enables the manufacturer to separate a substance from its contaminating materials or to alter certain of its physical properties such as its density, color, hardness, or solubility.

Drugs must be analyzed after they are manufactured to ensure both their identity and their purity. The analytical methods used may be either qualitative or quantitative. Regardless of the nature of the method, precipitation is likely to play an important role. Inspection of the tests for purity and identity and of the assay methods listed in the official monographs for the various substances described shows how much precipitation is relied upon. For example, one of the common tests for the identity of calcium salts involves proving the presence of the calcium ion through the formation of insoluble calcium oxalate when a solution of ammonium oxalate is added to a neutral or alkaline solution of the calcium preparation. The identities of the calcium salts of the Pharmacopoeia are confirmed in part by this precipitation method. A typical quantitative use of precipitation is made in the assay of magnesium sulfate. A solution of the sulfate is treated first with a solution of sodium phosphate, then with stronger ammonia test solution. A precipitate of magnesium ammonium phosphate is the result. This is then converted into magnesium pyrophosphate by heating. The weight of the pyrophosphate formed is converted to the equivalent weight of magnesium sulfate by means of a factor given in the Pharmacopoeia.

Precipitation is important in the preservation of medicines. In many drug products, deterioration is observed as they age

by a precipitate gradually accumulating at the bottom of the container. The deposit is usually a decomposition product formed by the slow chemical and physical changes in the active constituents of the preparation. If this precipitation could be prevented, loss of activity and changes in physical appearance could frequently be almost eliminated.

In the dispensing of medicines, precipitation often becomes important. Many times the ingredients in a prescription react with each other in solution to form insoluble compounds. Precipitates of this kind formed during compounding belong to a class of dispensing difficulties known as **incompatibilities.** Incompatibilities fall into three broad categories, (1) physical, which has to do largely with solubilities; (2) therapeutic, in which drugs of antagonistic physiologic action are called for in the same prescription; and (3) chemical, which involves the formation of undesirable color changes, gaseous products, and precipitates. Since the latter type of incompatibility sometimes is dangerous to the patient or, since if not dangerous, it may at least interfere with the normal therapeutic action of the medicine involved, its study is an important branch of pharmacy.

Certain of our medicines produce their therapeutic effects through precipitation. For example, astringent drugs frequently owe their medicinal virtues to their ability to precipitate protein material within tissue cells. Many antidotes for poisons are effective only because they react with the poison to produce precipitates, which, because of their insolubility, cannot further damage the body. A large group of antiseptics carry on their work of destroying bacteria by precipitating the cell contents. The more efficient treatments for severe burns require the application of protein precipitants to the areas denuded of skin. There are numerous other situations in which the mechanism of precipitation plays an important therapeutic role.

Diagnosis of disease is sometimes greatly facilitated by precipitation reactions. The clinical-laboratory technician performs tests on the various fluids of the body. In certain instances, positive or near-positive indications of disease are given by the appearance of characteristic precipitates. Diagnosis of diabetes is an excellent example of the clinical value of precipitation. One of its characteristic symptoms is a sugar-bearing urine.

When mixed with Fehling's solution the sugar reduces the copper sulfate to form first a yellow precipitate of cuprous hydroxide and then a red precipitate of cuprous oxide. The appearance of these precipitates is considered evidence of diabetes.

It should be apparent from these examples that some knowledge of the chemistry of precipitation is invaluable in pharmacy. The chemistry of the formation of simple precipitates is nicely illustrated by the uncomplicated series of equilibriums that are set up when solutions of silver nitrate ($AgNO_3$) and hydrogen chloride (HCl) are mixed. The ions of both compounds behave in accordance with the equations below:

$$\begin{array}{rl} AgNO_3 \rightleftharpoons & Ag^+ + NO_3^- \\ HCl \rightleftharpoons & Cl^- + H^+ \\ & \downarrow\uparrow \quad \downarrow\uparrow \\ & AgCl\downarrow \quad HNO_3 \end{array}$$

Of all the possible combinations of ions in these equations, the one forming silver chloride (AgCl) is the only one that is insoluble. It therefore separates from the solution in the form of a precipitate. For all practical purposes, the separation is complete, *i.e.*, all the silver chloride is removed from solution by precipitation. Actually, however, there is no such thing as complete insolubility, for even such insoluble compounds as silver chloride are somewhat, even if ever so slightly, soluble. Therefore, enough AgCl remains in ionized form to saturate the supernatant liquid. In this instance, the amount required to saturate the solution is small, for only about 0.000011 gram molecule of the dissociated compound is soluble in a liter of water at ordinary temperatures. Thus the reason is apparent why, for practical purposes, precipitation is considered complete.

Another example of formation of a precipitate involves the mixing of solutions of silver sulfate (Ag_2SO_4) and barium chloride ($BaCl_2$). The equilibriums reached in this mixture are shown in the following equations:

$$\begin{array}{rl} Ag_2SO_4 \rightleftharpoons & 2Ag^+ + SO_4^{--} \\ BaCl_2 \rightleftharpoons & 2Cl^- + Ba^{++} \\ & \downarrow \quad \downarrow \\ & 2AgCl\downarrow \quad BaSO_4\downarrow \end{array}$$

Both the silver chloride (AgCl) and barium sulfate ($BaSO_4$) are sparingly soluble, hence, both precipitate. As the precipitation proceeds, the solution is drained practically free of the required ions. We can see that if solutions containing molecular equivalents of silver sulfate and barium chloride are mixed it is possible to produce a filtrate of almost pure water. Pharmaceutical use can at times be made of this principle.

An understanding of the theoretical aspects of precipitation is facilitated by a discussion of **solubility product.** By definition, solubility product is the product of the concentration of the ions of a salt in a saturated solution. Formulated on a mathematical basis, the solubility product of a salt, $K_{s.p.} = B \times A$, where B and A are, respectively, the concentrations in gram-ions of the cation and anion.

How solubility-product values may be applied in precipitations can be shown by using a saturated solution of barium sulfate as an example. At ordinary temperatures such a solution contains about 2.3 mg. of barium sulfate per liter, which is equivalent to about 0.00001 gram molecule per liter. In this dilution the salt is completely ionized; so each ion will be present in a concentration of 0.00001 gram ion per liter. Applying our definition for solubility product to barium sulfate, we can now say that the value for that compound is equal to (Ba) $\times$ (SO_4), or $K_{s.p.} = 0.00001 \times 0.00001 = 1 \times 10^{-10}$. Whenever the product of the concentrations of the ions of barium sulfate exceeds the value of $K_{s.p.}$, precipitation takes place and continues until the value is restored. Values of this kind exist for saturated solutions of all other compounds having some degree of insolubility. Increase the concentration of any of the ions of these saturated solutions, and precipitation takes place until the appropriate value is restored. From this it can be generalized that whenever a pharmacist produces a precipitate it was done by exceeding the solubility product for the particular compound that is separated.

Crystallization.—Crystallization is any process that causes the ions, atoms, or molecules of a crystallizable substance to build themselves into definite solid geometric forms called **crystals.**

The commonest methods for bringing about this orderly building are as follows: (1) Cooling a liquid until it forms crystals

of itself and so becomes solid. The freezing of water is the outstanding example of this method. (2) Cooling a concentrated solution of a crystallizable substance. As the temperature lowers, the solution becomes supersaturated and crystals of the solute begin to form. (3) Evaporation of the solvent from the solution of a crystallizable substance. (4) Driving off dissolved gases. This really is not a common procedure, for there are relatively few instances in which a solid is held in solution by a gas that, if driven off, would liberate the solid. Nature furnishes two illustrations among the natural mineral waters. Insoluble ferrous carbonate and calcium carbonate are both dissolved in underground water by the action of carbon dioxide gas, which changes them to soluble bicarbonates; escape of the gas as the waters emerge from the ground permits the precipitation of the normal carbonates. (5) By chemical action between two or more substances to produce a new insoluble substance. The reaction between calcium chloride and sodium carbonate solutions to form calcium carbonate is typical. (6) By electrolytic deposition, more commonly known as electroplating. Extremely fine crystals are usually formed in this process. (7) By changing the character of the solvent. Typical is the addition of alcohol to an aqueous solution of sugar or ferrous sulfate. Neither substance is highly soluble in varying concentrations of alcohol; so when the original solvent is sufficiently diluted with that fluid, both begin to precipitate. One of the pharmacopoeial tests for the purity of lactose makes use of the ability of one fluid to throw a substance out of solution by alteration of the solvent. (8) By sublimation, which has been called crystallization from the vapor phase. Mercuric chloride and other compounds can be manufactured in this way. Iodine is purified by sublimation and for that reason is often labeled "resublimed iodine."

The Forms of Crystals.—The crystals of any given substance always form in accordance with a definite geometric pattern that, for the substance, is characteristic. Although there are literally thousands of crystallizable substances, their crystal forms can be resolved into only six fundamental geometric designs, called **crystal systems.** This is possible because every crystal is bounded by plane surfaces called **faces,** which make

characteristic **angles** at their points of intersection. Imaginary lines drawn through the center of the crystal and connecting the centers of opposite faces or the tips of opposite angles are the axes of the crystal. By making use of these characteristics, crystallographers have developed the six basic systems, which are now briefly described.

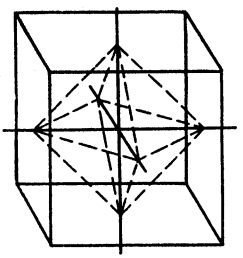

FIG. 103.—Cubic system.

1. **Cubic, regular, or isometric** system (Fig. 103). These crystals have three axes of equal length intersecting each other at right angles. Sodium bromide is a member of the cubic system.

2. **Tetragonal** system (Fig. 104). These crystals have three axes; two of these are equal in length and intersect each other at right angles, and the third intersects the plane of the other two at right angles but is either longer or shorter than they. Urea belongs to this system.

3. **Orthorhombic** system (Fig. 105). These crystals have three unequal axes intersecting each other at right angles. Iodine is an example.

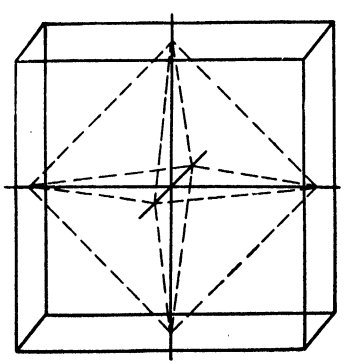

FIG. 104.—Tetragonal system.

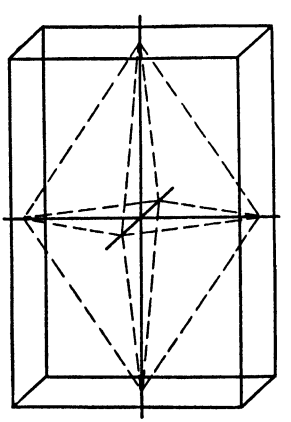

FIG. 105.—Orthorhombic system.

4. **Hexagonal** system (Fig. 106). These crystals have four axes, three of which are equal, lie in the same plane, and intersect each other at 60-deg. angles. The fourth lies at right

angles to these three. Calcium carbonate is a member of this system.

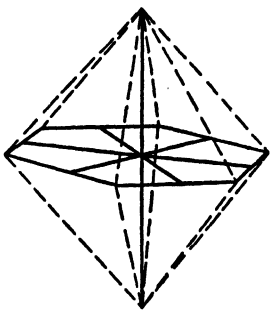

FIG. 106.—Hexagonal system.

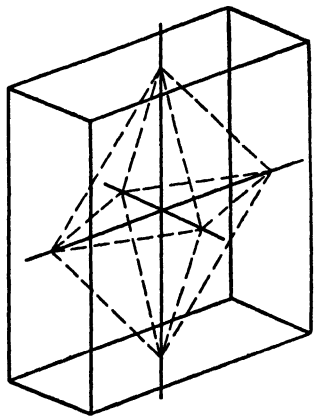

FIG. 107.—Monoclinic system.

5. **Monoclinic** system (Fig. 107). These crystals have three unequal axes, two of which are oblique and the third perpendicular to the oblique axes. Tartaric acid is an example.

6. **Triclinic** system (Fig. 108). These crystals have three unequal axes all obliquely inclined to each other. Boric acid is an example.

Water in Crystals.—Many compounds combine with water to form new compounds that are crystallizable. Crystals so formed are called **hydrates,** and the compound with which the water has combined is said to be **hydrated.** The water, held in true chemical combination, is called **water of hydration** or **water of crystallization.** Before combining with the water the compound is said to be **anhydrous.**

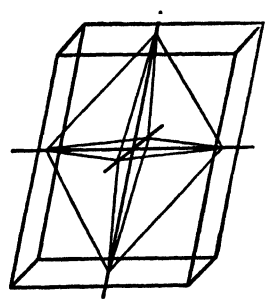

FIG. 108.—Triclinic system.

A number of the official medicines are hydrates. Copper sulfate is an example. It combines with five molecules of water to produce a compound the composition of which is expressed by the formula $CuSO_4 \cdot 5H_2O$. The [·] between the two simple formulas indicates that the molecules are loosely combined.

Confusion should be avoided between the term **interstitial water,** which is water held mechanically in the crevices of interstices of the crystals, and water of crystallization, which is held chemically. When crystals holding interstitial water are heated, the moisture in the crevices expands with sufficient rapidity to cause miniature explosions. This phenomenon is called **decrepitation.** Sodium chloride shows this property.

Some hydrates, at ordinary temperatures, will spontaneously give up to the atmosphere the water they contain. Crystals doing this are said to **effloresce** or to be **efflorescent,** and the process is called **efflorescence.** In perfectly dry air, all hydrates will effloresce because the air has no aqueous vapor pressure to offset even a small vapor tension of the hydrate. This is usually accompanied by loss of crystal structure to form opaque powders. This property is shown by official magnesium sulfate.

The opposite of efflorescence is **deliquescence.** Some substances spontaneously absorb water when they are exposed to an atmosphere that is not perfectly dry and become hydrated. This phenomenon is called deliquescence. If the vapor tension of the atmosphere is sufficiently high, the absorption of water will continue until the compound has gone completely into solution. Substances withdrawing water from the atmosphere in this fashion are said to be deliquescent (or hygroscopic), and while they are undergoing the transformation they are said to deliquesce. (See Chap. X also.)

Recrystallization.—One of the most widely used methods for purifying solids is by recrystallization from a suitable solvent, usually water. Many drugs are changed in this way from highly contaminated substances into chemicals of pharmacopoeial quality. If magnesium sulfate, for example, containing a small amount of some other soluble material as an impurity is dissolved in enough hot water to make a saturated solution and is then allowed to cool, it will usually precipitate with a much smaller amount of impurity. It is obvious that if the process is repeated several times the sulfate will soon be relatively free of the contaminant.

Granulation.—Granulation is the process of producing coarsely grained particles, usually irregular in shape. It has also been defined as **interrupted crystallization,** carried on in such fashion

that sabulous or coarse-grained powders are produced. The latter definition is the narrower in conception since it obviously must be restricted to certain precipitation methods.

In pharmacy, granulation may be carried on by physical as well as by chemical means. Whatever the means, the irregular particles produced have certain pharmaceutical advantages.

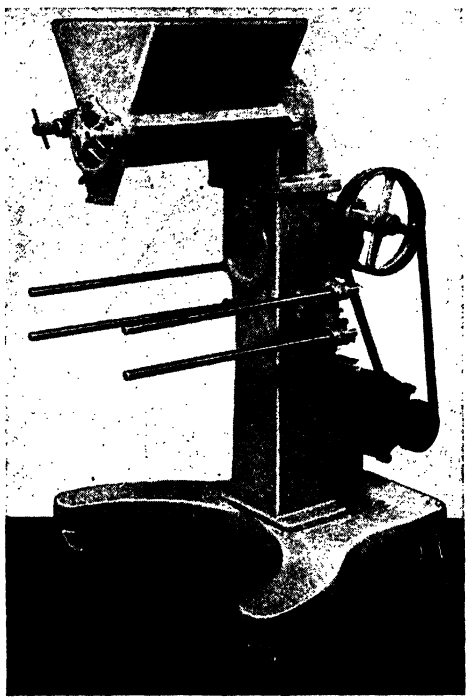

FIG. 109.—Granulator for tablet granulations. Used in large-scale tablet manufacturing. (*Courtesy of F. J. Stokes Machine Company.*)

Tablet manufacturers could not function without methods of granulation. A few chemicals can be compressed into satisfactory tablets without any preliminary treatment except the incorporation of a lubricating substance, which enables them to pass through the tablet machine better. On the other hand, the majority of chemicals must be granulated before they can be compressed properly into tablets. Here the process of granulation consists in moistening the substance with water, diluted alcohol, syrup, or some other suitable excipient first, in order to

make a mass. The mass is broken into smaller pieces and dried in some sort of oven. The dried lumps are then either sifted to uniform size directly or ground and sifted. Granulation in the making of effervescent salts is carried on in essentially the same way.

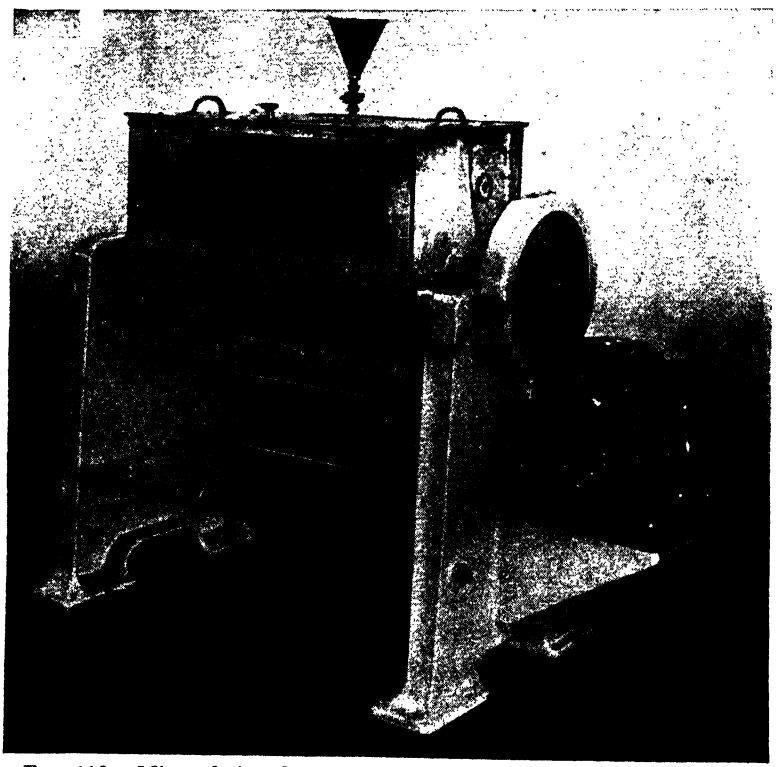

FIG. 110.—Mixer designed to facilitate the preparation of tablet granulations, etc., in large commercial operations. (*Courtesy of F. J. Stokes Machine Company.*)

Granulated Opium of the Pharmacopoeia is made by a special milling and sifting process designed to give a coarse rather than a fine powder. The larger particles are more suitable for use in the preparation of the various liquid extracts of opium. The coarse powder lends itself better to extraction.

Chemicals in granular form are sometimes more soluble than when precipitated with a more nearly perfect crystalline form.

STUDY QUESTIONS

1. Define precipitation.
2. Discuss the importance of precipitation to pharmacy.
3. Illustrate by ionic equations how precipitation reactions take place.
4. What is solubility product?
5. List five ways of inducing crystallization.
6. Why is the name *corrosive sublimate* a logical one for mercuric chloride?
7. What is a crystal axis?
8. Give two points of difference between the cubic and tetragonal crystal systems.
9. How does efflorescence differ from deliquescence?
10. What is interstitial water?

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CHAPTER XVII

MECHANICAL SUBDIVISION OF DRUGS

Solid drugs in their crude or unprocessed forms assume a wide variety of physical shapes. Frequently neither the shapes nor the sizes of the original pieces are suitable for the manufacture of or for use in medicinal preparations. It therefore becomes necessary to alter the physical condition of the drug. Often the process of alteration is one of subdivision; the original pieces or particles are simply made smaller.

At first glance, the problem of subdividing drugs appears to be relatively free from complications. It would seem a simple matter to reduce a large piece of material to a number of smaller pieces; however, the various types of substance to be broken up introduce a variety of difficulties. These are the result of nature's vagaries in making some solids hard, others brittle, still others gummy, some slippery, some deliquescent, and so on. Each of these physical characteristics must be taken into account when plans for subdividing are being made. It is easier to understand more fully why the physical and sometimes the chemical properties of drugs are so important in the problem of subdivision, if we know more concerning the manner in which they interfere with the process.

Illustrations abound; they are almost as numerous as the substances to be broken up. A few examples will be sufficient to clarify the situation and furnish the tools for working out an understanding of the entire field of subdivision. Certain vegetable drugs in their crude form contain a high percentage of gummy material, which makes their fragmentation by grinding a difficult task. Others are fatty in nature and present the same type of problem in grinding. Preliminary removal of the interfering substances is frequently carried out before the major dividing process is begun. Animal drugs, because of the peculiar nature of the organic material comprising them, often require

such individual treatment as freezing, desiccation, or both, before being finally subdivided. Generally speaking, the least troublesome of all drugs are those of mineral or synthetic origin. The major difficulties here are those of hardness or susceptibility to chemical change due to increased surface exposed after subdivision to the action of air, moisture, light, and heat. Occasionally, a drug like boric acid, which is unctuous or very slippery, causes trouble because of that property, but such instances are exceptional.

From the examples given illustrating the importance of the properties of drugs in relation to the problem of their subdivision, it can be appreciated that more than one method of subdividing must be available. Variety in the methods used makes mandatory a variety in equipment. The student of the problem, therefore, must not only know the properties of the drugs being broken up but also the best method and best machinery for the purpose.

Ordinarily, the retail pharmacist need not concern himself with the more complex phases of drug subdivision. For him the spatula, mortar and pestle, and muller usually suffice. It is the manufacturing pharmacist who must be familiar with all the intricacies of technique and types of machine designed for this task. Several of the machines used in manufacturing that involve basic designs and principles will now be described.

Ball Mills.—These mills are cylinders so supported that they can revolve horizontally on their long axis. Into the cylinder is fed the substance to be subdivided, together with rounded flints, pebbles, and Porox or steel balls, which act as the grinding agents. The cylinder is set in motion. As the mill revolves, the pebbles or balls are carried upward along its surface. When a certain point is reached, the grinding mediums tumble down the inclined plane, breaking up the drug as it goes.

The efficiency of this method depends on the number of balls or pebbles tumbling within the mill and the extent of inside surface of the cylinder itself. It is possible to obtain more grinding surface in a properly balanced ball mill than in any other type of grinder. It is therefore correct to say that this machine uses one of the most efficient grinding principles known.

Another advantage claimed for the ball type of mill is that it occupies less space per unit of output than other forms of grinder. It also requires less power to operate and a minimum of attention or labor to maintain. The latter advantage is due to the fact that no adjustment, or dressing, of grinding surfaces is required.

Construction.—The basic construction of a ball mill hinges on the principle of a revolving cylinder and to that extent is similar in all machines of this kind. For heavy duty and large outputs, the mills are usually made of substantial high-carbon or chrome manganese steel. Bronze, stainless steel, and other metals are used for special purposes. For smaller laboratory use, the cylinders can be either steel or Porox jars. The smaller

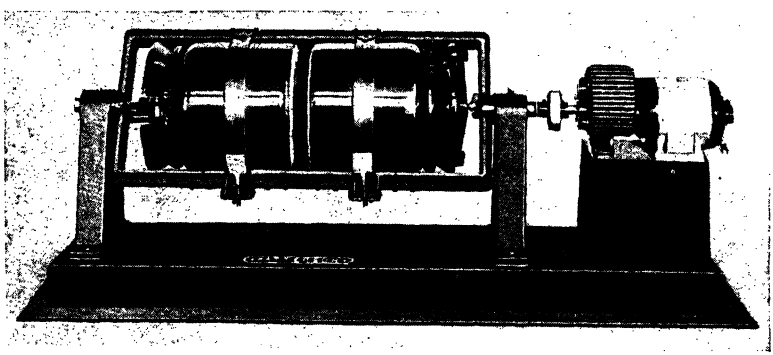


FIG. 111.—Ball mill. (*Courtesy of Patterson Foundry & Machine Company.*)

machines can be built to hold more than one jar. These little mills are frequently called **jar mills** because the cylinder units so closely resemble large jars or crocks. Cylinders can be lined with a variety of nonferrous materials if it is desired. Some of the lining materials used are porcelain, buhrstone (silex), rubber, and wood.

Special construction to provide for either high or reduced pressures while the mill is in operation is also possible. Provision can be made for such features as drying, aerating, distillation, recovery of solvent, gas absorption, and chemical reaction during the grinding operation. The mills can also be jacketed to permit circulation of steam, hot oil, cold water, or brine for controlling the temperature of the operation. One manufacturer makes a mill with a patented thermal control of this type that

will produce temperatures as high as 500°F. Temperature control is frequently important in grinding operations. Some substances tend to solidify when cold. Heating prevents this congelation, or an increase in consistency. On the other hand, in grinding substances that are injured by heat, it is advantageous to keep them very cold during the process.

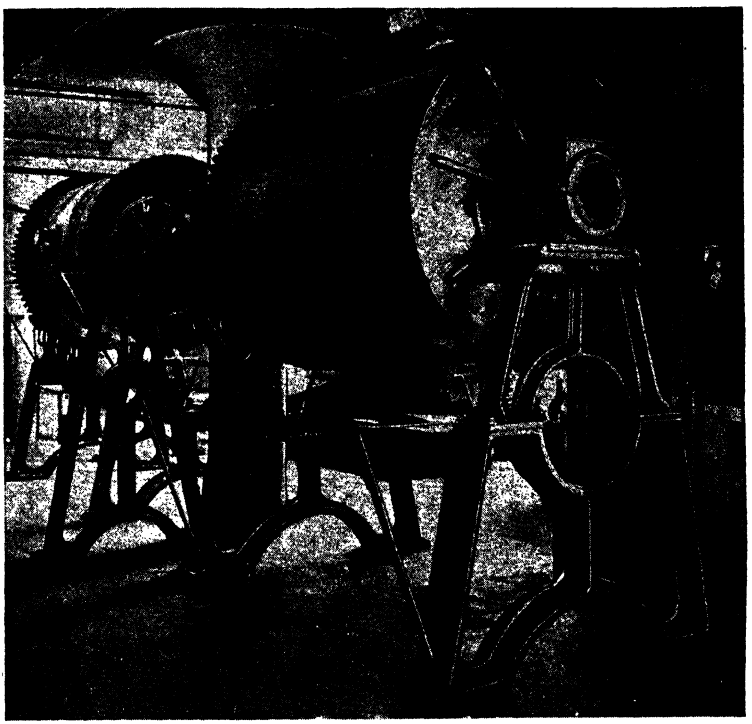


FIG. 112.—Heavy-duty pebble mill. (*Courtesy of Patterson Foundry & Machine Company.*)

Provision can also be made for continuous grinding. In mills designed for this purpose, the material to be subdivided is fed continuously through a hollow trunnion at the feed end of the mill and is discharged continuously through the trunnion at the opposite end.

Pebble mills are basically ball mills but may differ from them in construction. The name is probably the result of the widespread use of stones as the grinding medium.

Pot mills are a variety of ball mill, the hopper being shaped like a pot rather than a jar and rotating on an axis set at an angle of about 45 deg.

Stone mills are also modified ball mills. They are designed to handle ointments, tooth pastes, massage creams, and other pastes requiring very fine grinding.

Tube mills, basically, are ball mills in which the cylinder has an exaggerated length in comparison with its diameter.

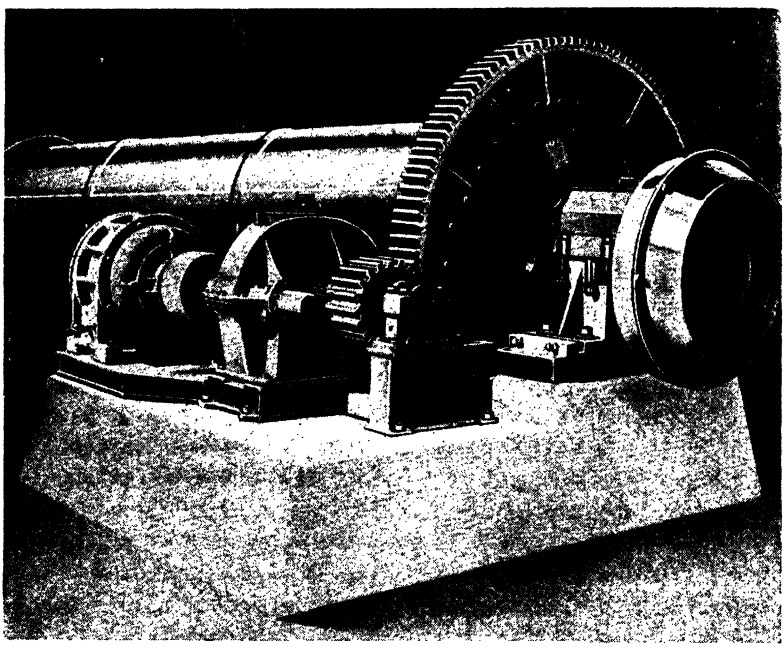


FIG. 113.—Tube mill. (*Courtesy of Abbe Engineering Company.*)

Ball mills, generally speaking, are those whose lengths are approximately equal to their diameters. A considerable increase in length without appreciable change in diameter converts it into a tube mill.

Crushers.—Crushing machines such as the **saw-tooth crusher** take advantage of the shearing power developed by intermeshed star-pointed saws when they are made to revolve toward each other. In general, they consist of a hopper inside of which is placed the crushing mechanism. This consists of two steel

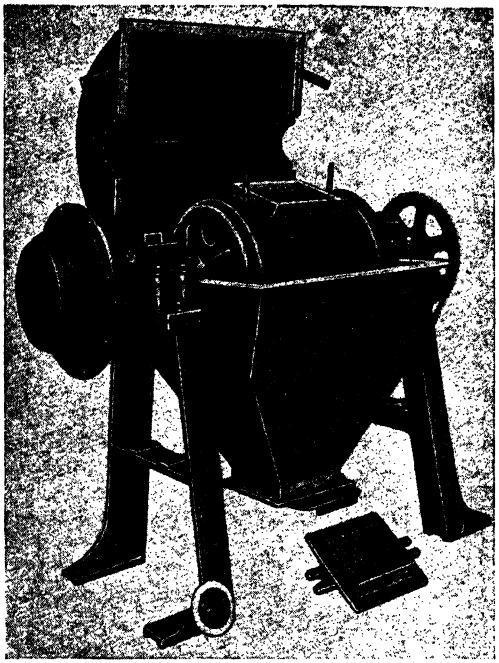


FIG. 114.—Small tube mill for continuous dry grinding. (*Courtesy of Abbe Engineering Company.*)

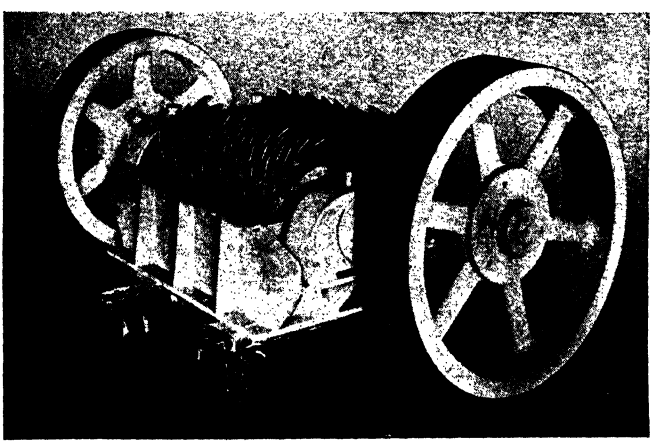


FIG. 115.—Saw-tooth crusher. (*Courtesy of Abbe Engineering Company.*)

shafts which revolve toward each other and on which are mounted a number of heavy steel star-pointed saws so spaced as to intermesh. The width of the spacing and the fineness of the teeth in the saws regulate the maximum size of the crushed product.

Machines of this design are recommended for reducing many kinds of bulky materials to proper uniform size so that they will feed readily into grinding or pulverizing machines.

Spiral-roll crushers are hopper-type machines that use two hardened spiral rolls as the crushing medium.

Cone-type crushers make use of interlocked cones both of which are geared so that with proper meshing an effective grinding surface is provided.

Steel Knife Cutters.—These machines, designed for cutting such substances as roots and barks, consist of the usual hopper in which is fitted a cutting device. The device is usually a solid steel rotor carrying about five firmly attached revolving blades or knives. Surrounding the rotor is a cage to which stationary knives are attached. Fitted with screens having mesh of the proper perforations, the machine can be set to produce coarse, medium, or fine grades of material.

Attrition Mills.—Mills of this type are much recommended for vegetable substances. The machine operates by means of two grinding disks, or plates, which are interchangeable in order to give the mill flexibility in operation. They are constructed on the same principle that is incorporated in dressing an old-fashioned burr; that is, they have a bosom in the body of the plates, causing them to make a gradual reduction from the time the stock enters the machine until it is finished. The materials can thus be ground to a fine and uniform particle size without too much packing. This makes for a light bulky product. Particle size can be varied through a reasonable range from fine to coarse.

Disintegrators.—Machines of this kind are designed for the subdivision of dry nonfibrous materials by beating. The beating device is somewhat more complex than is found ordinarily in subdividing machines. It consists of hardened-steel beaters securely riveted onto the face of a steel disk. As the disk revolves, the beaters pass between corrugated rings, catch the material to be broken up as it enters the mill, and beat it against

the corrugations until it is fine enough to pass between the rings and the disk to the discharge side of the mill. Here a set of backbeaters, riveted onto the reverse side of the disk, beat the material against a screen until it is fine enough to pass through. The screens, of hardened square-cut steel, extend three-fourths

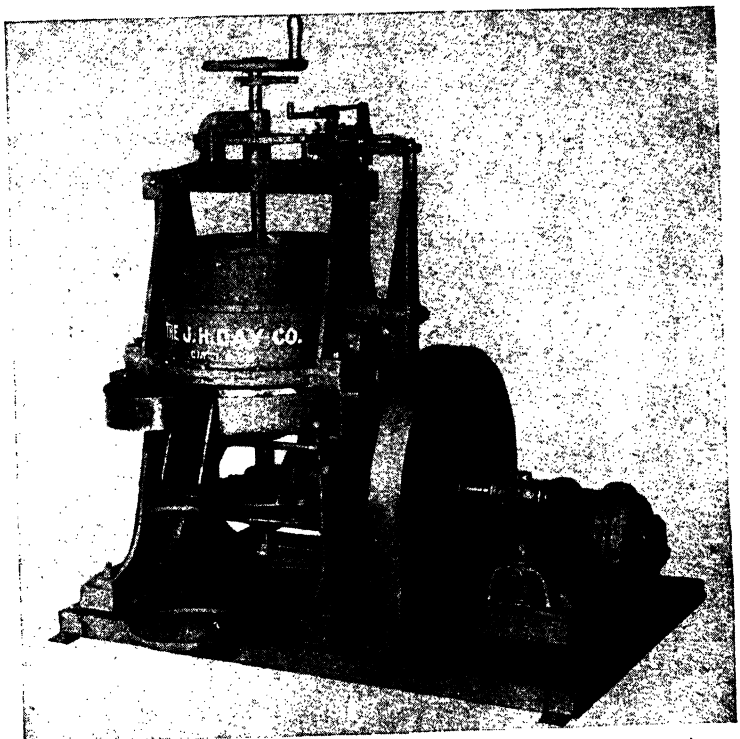


FIG. 116.—Ointment mill. (*Courtesy of The J. H. Day Company.*)

around the diameter of the disk. This furnishes a large grinding and discharge surface.

Ointment Mills.—There are various types of mill built for grinding unctuous materials. The stone mill already described is one of these. Many of the machines make use of the principle of two grinding plates. Others cause the material to be ground to pass between hollow chilled rolls.

Colloid Mills.—As the name implies, colloid mills are designed principally for the purpose of dispersion of one immiscible sub-

stance throughout another. They are largely used, therefore, for pharmaceutical emulsions and colloidal dispersions such as the various oil emulsions and milks, or magmas. The machines produce a fine blending of materials and the ultimate reduction in the size of particles. Liquids must always be a part of the ingredients used.

FIG. 117.—Colloid mill, interior view. See Fig. 118 for a diagrammatic study of the side view. (*Courtesy of Chemicolloid Laboratories, Inc.*)

The working principle of the mills is based on the hydraulic shearing power that can be produced in a very thin film of liquid. This shearing effect is obtained by drawing the liquid into the narrow space between a rotor revolving at high speed and its jacketlike stator. Tremendous shearing forces are set up within the film under the influence of the high speed of the rotor on the inside and the stationary stator on the outside. Both solid and liquid particles present in the film are broken up into microscopic dimensions. Use of this basic principle makes it possible

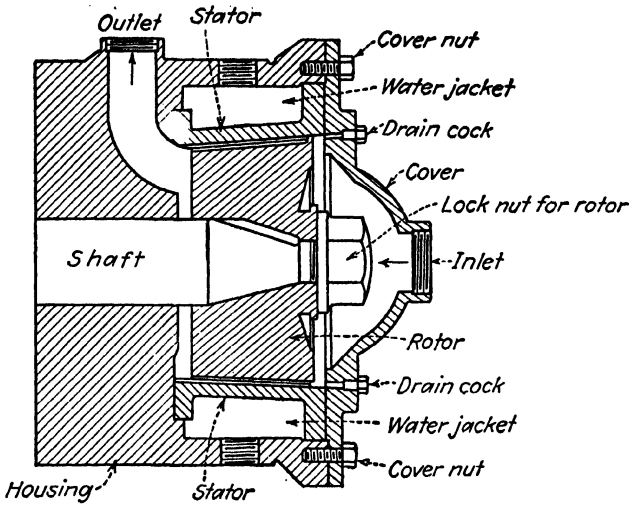


FIG. 118.—Side view of colloid mill shown in Fig. 117.

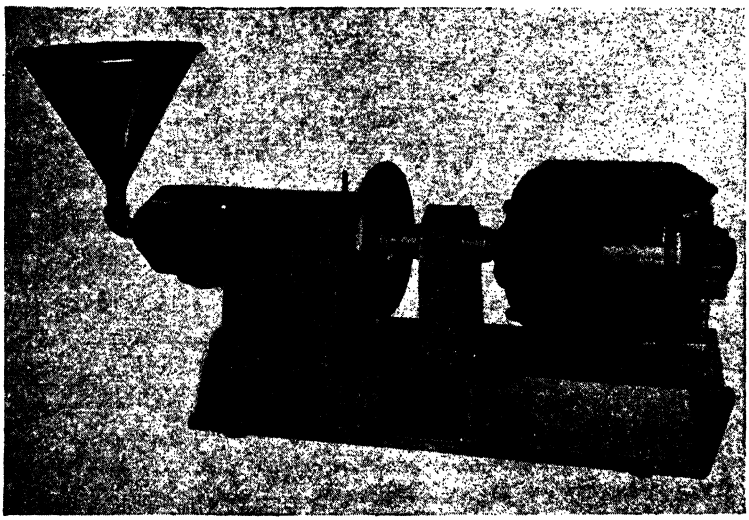


FIG. 119.—Charlotte colloid mill. (*Courtesy of Chemicolloid Laboratories, Inc.*)

to mill immiscible liquids, liquids containing solids in suspension, and pastes to the point at which they are so finely dispersed and homogenized that remarkable smoothness can be imparted to the finished products.

The newer machines of this type run at very high speeds. Some of the smaller belt-driven units will run as high as 17,000

FIG. 120.—Triple-action colloid mill. (*Courtesy of C. O. Bartlett & Snow Company.*)

FIG. 121.—Paste-type colloid mill. (*Courtesy of Premier Mill Corporation.*)

revolutions per minute (r.p.m.). As speeds have been increased, designs have been simplified to the point at which the mills usually have only one moving part (the rotor) and one adjustment, a micrometer arrangement regulating the gap between the rotor and stator. Mills so designed whirl the material in such a fashion as to subject it to a high-velocity impact that breaks it up into minute particles or globules. It is then mechanically

sheared by the teeth in both the rotor and the stator. Then it is hydraulically sheared by the smooth surfaces of rotor and stator. Some of the mills have water jackets for thermal control that enable the operators to handle substances sensitive to or affected by heat without deterioration.

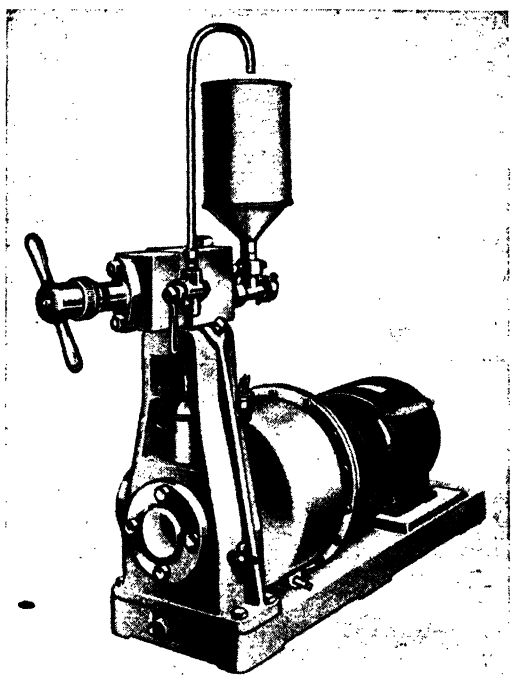


FIG. 122.—Colloid mill or laboratory homogenizer. (*Courtesy of Mauton-Gaulin Manufacturing Company.*)

Homogenizers.—These are machines for emulsifying and dispersion, just as are colloid mills. Their dispersing action is produced by high pressure, in contrast to the colloid mill, which accomplishes its purpose through the contact of the material to be dispersed with parts moving at high speeds and at clearances measuring 0.001 to 0.0125 in. The principle of action is that of the simple plunger-type pump which forces the product being emulsified or dispersed between a valve seat and valve. The high pressure built up ahead of the plunger furnishes high

velocity and hydraulic shear sufficient to produce dispersion particles having diameters of one micron or less.

Hand-operated homogenizers of small capacity are used in some pharmacies as emulsifiers. They are quite effective (see Chap. XIV).

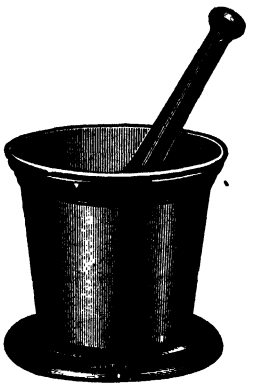


FIG. 123.—Iron mortar of the type suitable for contusion.

The machines and processes just described are for the most part used in manufacturing plants. Other large-scale mills such as edge-runner mills are used, also. Subdividing problems that must be handled in the pharmacy usually can be solved by one of the following procedures, which require very little and relatively inexpensive equipment. Three of the methods, contusion, precipitation, and elutriation, although useful, are not common techniques for retail pharmacists; in fact, precipitation, strictly speaking, is not a mechanical procedure for subdividing drugs. The others are used in the daily routine of most stores.

Contusion.—Contusion (from the Latin, to break or to beat) is the process of subdividing a drug by pounding or bruising it. This is usually done in a heavy, deep metal mortar by means of a stout, heavy pestle. Fortunately for the retail pharmacist, most of the drugs requiring such treatment before use can be purchased already processed from manufacturers. Most pharmacies, therefore, are not equipped with mortars of suitable construction.

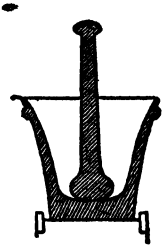


FIG. 124.—Cross section of an iron mortar and pestle.

Where the operation of contusion is to be carried out, the mortar should be placed on a heavy block of wood or embedded in sand to absorb the shock of the impact of the pestle and to prevent unnecessary noise in the laboratory.

Trituration.—One of the important techniques in pharmacy is trituration (Latin *tritura*, a rubbing), which is the process of reducing substances to a fine powder by grinding them in a mortar with a pestle. Substances already in a fine state of sub-

division can be combined in a uniform mixture by means of trituration. Thus the term has more than one connotation, but the equipment required is always the same.

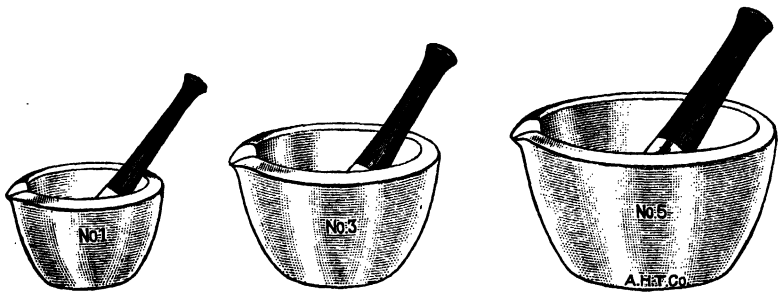


FIG. 125.—Wedgwood mortars.

The mortars in which the grinding is to be done are heavy concave dishes of the general shapes shown in Figs. 125 to 128. They are constructed of wedgwood, porcelain, or glass. Occasionally a small iron or brass mortar will be found in use, and for very delicate quantitative operations tiny mortars of agate are necessary. For general use, however, porcelain and wedgwood are adequate. Mortars are stained by certain medicinal chemicals such as iodine by absorption into their microscopic pores. Glass mortars are best in such circumstances.

FIG. 126.—Porcelain mortar.

The degree of curvature of the interior of the mortar is not so important as the choice of pestle to be used. The pestle is of the

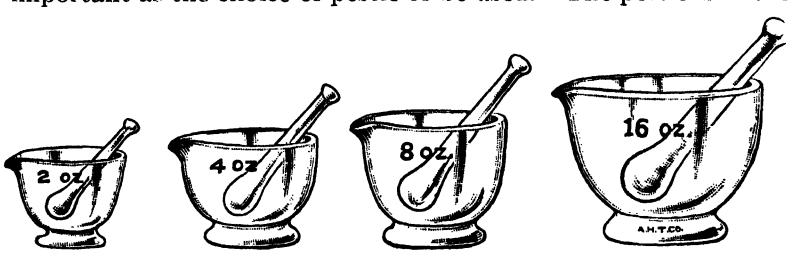


FIG. 127.—Glass mortars. Of particular service when a nonpermeable grinding surface is desired.

same material as the mortar and like a short baseball bat with a swollen tip. (See Fig. 127.) Its point of contact with the floor of the mortar represents the available active grinding

surface in the process of trituration. The curvature of the tip of the pestle and mortar surface should therefore be similar.

The act of trituration is carried on by moving the pestle in a circular motion, exerting pressure all the while on the powder being processed. The circle can start from the center of the mortar and gradually be enlarged by working toward the mortar walls, or it can start at the outer edge and be gradually lessened in diameter as shown in Fig. 129.

FIG. 128.—Agate mortar for triturating very small quantities of material, particularly samples for quantitative analysis.

Regardless of the direction of motion chosen for the trituration, a certain amount of the powder will cling to the sides of the mortar or the head of the pestle. It is thus eliminated from the grinding and should be dislodged. This is accomplished by the use of a spatula.

Spatulas are usually short, flexible steel blades to which are affixed wooden handles. The blade, commonly 4 to 6 in. in length and ½ in. wide, can be pushed around the interior of the mortar so that it conforms to the curved surface and slices or scrapes off the adhering powder, which falls toward the center, where it can be once again crushed under the pestle. For special purposes, spatulas are made of porcelain, horn, rubber, etc. Iodine attacks iron, which makes it necessary to use a

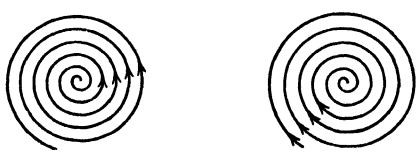


FIG. 129.—Direction of pestle movements in the act of trituration.

rubber or other nonreacting spatula whenever it is present in a triturating process. Stainless-steel spatulas are much less susceptible to chemical reactions and so can be more widely used than the common steel spatula.

Precipitation.—Substances are sometimes subdivided by precipitation. The material of unsatisfactory size or form is put into solution and then precipitated under controlled conditions to the particle size desired.

Elutriation, or water sifting, is really a process of segregation. **It is discussed in Chap. XVIII, page 525.**

Levigation.—Some materials that are already powdered are conveniently subdivided further by rubbing them on a slab or in a shallow mortar in the presence of a liquid that has no solvent effect on them but merely moistens them. This is also known as **porphyrization,** or as **mulling** if conducted on a slab with a muller. The muller should be moved over the surface of the slab in either figures of eight or circles. The word *porphyrization* refers to the porphyry (purple stone slab) originally used in the process. (See also Chap. XVIII, page 526.)

Pulverization by Intervention.—Certain drugs such as camphor and boric acid are difficult to powder when triturated alone. Both powder easily if they are put in partial solution with a little alcohol. Use of an intermediary substance in this fashion to facilitate subdivision is called pulverization by intervention. The basic requirement is that it shall be easily removable after its period of usefulness is over.

STUDY QUESTIONS

1. Explain why the subdividing of a drug is not always a simple matter.
2. What is the principle upon which ball machines operate?
3. Name some of the conditions that may be controlled during grinding operations with a ball machine.
4. How does a tube mill differ from a pebble mill?
5. What is a rotor?
6. Explain the difference in operating principle between ointment and colloid mills.
7. How large in inches is a micron?
8. What is another name for elutriation?
9. How are the triturations of the Pharmacopoeia made?
10. Describe the process of levigation.

COLLATERAL READINGS

Catalogues and bulletins of manufacturers.

CHAPTER XVIII

SEPARATION OF SUBSTANCES BY MECHANICAL MEANS

SOLIDS FROM LIQUIDS, LIQUIDS FROM SOLIDS

This chapter deals with the separation of substances, usually without involving chemical reactions. Although substances may be separated from each other by chemical means, as is the case in precipitation, in most instances it is necessary to resort to mechanical means to accomplish this process.

Expression

Expression (Latin *ex*, out, + *premere*, to press), sometimes called forcible straining, is a process involving the removal by force of a liquid from a solid; it is the application of strong pressure to a mixture or a solid substance for the purpose of separating the liquid from the solid bodies. It permits the separation of a solid or a moist body from a liquid, *e.g.*, the liquid contained in the inner spaces of cellular matter. In general, the amount of liquid to be removed is small compared with the amount of solid obtained.

In the laboratory, the process is often resorted to in the removal of saps from fresh plants and juices from fruits for the preparation of syrups and other vehicles. It is used also to recover menstruums (solvents) from moist, exhausted powders (marcs) as in the preparation of tinctures, fluidextracts, extracts, etc.

Historical.—Possibly the term **expression** was first used in the thirteenth century by Lanfrance, an Italian surgeon, in his "Chirurgia magna et parva,"[1] a treatise on surgery. In 1660, Robert Boyle, the celebrated Irish chemist, used the word with its present meaning.[2,3] The most primitive method of expression was apparently the placing of seeds to be crushed in a mortar and mashing them until the oil was forced out. An advance in

[1] Joseph Thomas. "Universal Pronouncing Dictionary of Biography and Mythology," J. B. Lippincott Company, Philadelphia, 5th ed., p. 1484, 1930.

[2] *Ibid.*, p. 451.

[3] James A. H. Murray. "A New English Dictionary," Oxford University Press, New York, 1908, Vol. 3, Part 2, p. 446.

the process was made when fruit was first packed in sacks and covered with flat wooden surfaces on top of which stones were placed in order to expel the oil. Another early method was the grinding of seeds between stones, as is still done in India.[1] In the Orient, from the earliest times, many ingenious contrivances employing the principle of the lever and the wedge have been used for expressing oil from seeds and fruits, these oils for centuries having served as articles of food. Such implements have been gradually improved until we have today highly efficient hydraulic and screw presses; however, in the more backward countries, some of the oldest and most primitive methods are still in use for the drawing out of such oils as olive and palm.

The Chinese employed the same operations as are carried out in our most modern mills of grinding the seeds to a meal, using edge-runner mills, and expressing the oil in a wedge press. The Japanese used a special wooden press called *ta tsugi*. In Manchuria, after 4,700 years, these processes are still being carried out in a primitive form in the production of soybean oil.[1] In West Africa, simple hand presses are being used as they were generations ago.[2] It was a woman who first derived oil by packing olives in a sack and weighting with stones; she may be considered as the forerunner of the inventors of the present power presses.[3] Oils obtained by expression were often referred to in the Bible, the Ebers Papyrus, and other historical documents.[4] The Apocalypse of Moses contains a legend asserting that Adam, in the garden of Eden, knew of olive oil, probably as the first product of expression.[5] Babylonian medical texts reveal the earliest known methods used in preparing medicines, of which one was expression: "Juices expressed from herbs were often directed to be used . . . " in conjunction with wine as a base for certain medicaments of that time.[6] The oldest records of the Egyptians and the Hebrews reveal that they used this method to extract the juice of grapes for wine.[7] Wine presses are frequently mentioned in the Bible. Castor oil, expressed from the seeds, was familiar to the Egyptians, as it was mentioned in the Ebers Papyrus.[8]

[1] JULIUS ISADOR LEWKOWITSCH. "Chemical Technology and Analysis of Oils, Fats, and Waxes," Macmillan & Company, Ltd., London, 6th ed., 1929, Vol. 2, pp. 2, 3.

[2] "The Encyclopedia Britannica," 14th ed., 1929, Vol. 16, p. 749.

[3] CHARLES AINSWORTH MITCHELL. "Oils," Sir Isaac Pitman & Sons, Ltd., London, 1910, p. 4.

[4] C. J. S. THOMPSON. "The Mystery and Art of the Apothecary," J. B. Lippincott Company, Philadelphia, 1930, p. 15.

[5] A. C. WOOTTON. "Chronicles of Pharmacy," Macmillan & Company, Ltd., London, 1910, Vol. 1, p. 58.

[6] THOMPSON. *Op. cit.*, p. 1.

[7] JAMES MEW and JOHN ASHTON. "Drinks of the World," Scribner and Welford, New York, 1892, p. 12.

[8] CHARLES H. LAWALL. "Four Thousand Years of Pharmacy," J. B. Lippincott Company, Philadelphia, 1927, pp. 428–429.

Pliny, the famous Roman historian who lived immediately after the time of Christ, gives a detailed description of the screw presses used by the Romans in the production of olive oil.[1] The wine press, invented by the Assyrians, was used as much for making olive oil as for making wine and found its way from the south to the north of France, where it was commonly used for expressing poppy, hemp, and rape seeds.[2] Marco Polo, the celebrated Venetian traveler, mentions the manufacture of sesame oil by the expression of the seeds in Abyssinia and Ceylon and on the Malabar coast.

One of the most important contributions to the development of expression was the invention of the Dutch stamper press in the seventeenth century, which was used almost exclusively in Europe for pressing oily seeds until the early nineteenth century. The hydraulic press was invented in 1795 by Joseph Bramak and was perfected by George Armstrong in 1842.[3] The principle of this press was known for centuries, but its development is comparatively recent. The first hydraulic presses were little more than Dutch stamper presses in which hydraulic power was substituted for the wedge and falling weights.[4]

In this country the first oil mill using expression was erected in South Carolina in 1826. In 1870, peanuts were expressed to obtain the oil, which was mixed with cottonseed oil and sold for olive oil.[5] While it is apparent that the process is now only of minor interest to pharmacy, it was historically important as one of the first methods of extraction.

Expression is accomplished by **hand** and by **presses.** When the former method is used, a **strainer cloth,** usually of durable material such as a superior grade of muslin, is supported on a **holder (tenaculum)** or a funnel of suitable size. The material to be expressed is transferred to the cloth; any excess of liquid is allowed to drain off, the strainer is removed, and the cloth, with the included mass, is wrung until no more liquid is expelled.

In the laboratory, the process may be carried out by **mechanical means** using presses. These in their simplest form are known as **tincture** or **screw** presses (Fig. 131). The material to be expressed is placed in a container made of calico, muslin, horsehair, felt, or wool and then placed in the press. Pressure should be applied gently and gradually. This is especially true if the mixture is quite fluid, for it will act as a liquid and is almost

[1] "The Encyclopaedia Britannica," 14th ed., 1929, Vol. 16, p. 749.

[2] LEWKOWITSCH. *Op. cit.*, p. 205.

[3] *Ibid.*, pp. 6, 7, 10.

[4] T. W. CHALMERS. "The Production and Treatment of Vegetable Oils," D. Van Nostrand Company, Inc., New York, 1920, pp. 9–10, 56–82.

[5] DAVID WESSON. "History and Development of the Cottonseed Oil Industry in America," *Am. Inst. Chem. Eng.* **12,** 119 (1919).

incompressible. Consequently, if the pressure is applied too vigorously at the beginning, the bag is apt to rupture, or the press is subjected to undue strain, and the solid and liquid will both be expelled. After the bulk of the liquid is forced out, pressure may be increased.[1]

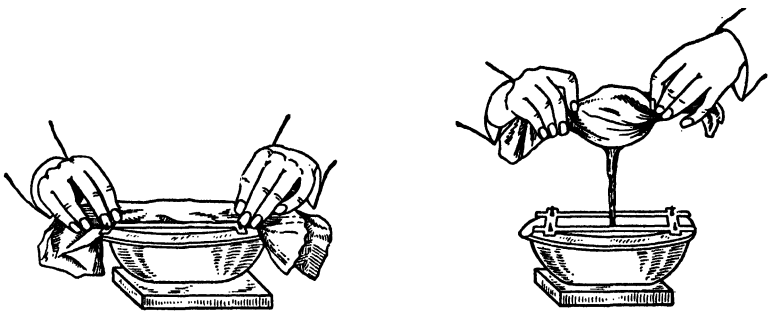


FIG. 130.—Simple expression.

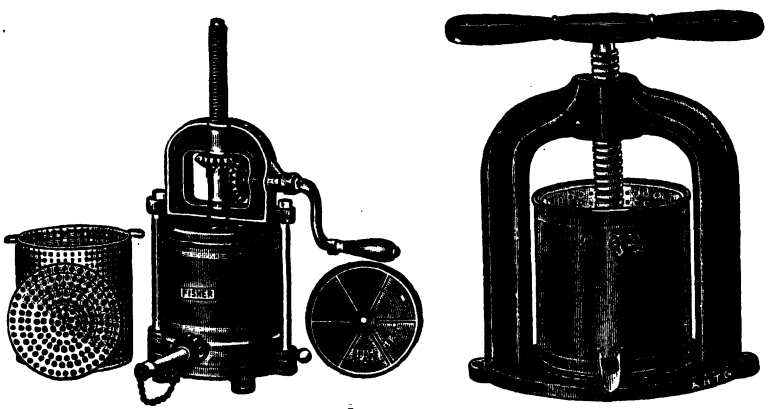


FIG. 131.—Screw presses.

Hydraulic Presses.—This form of press may be operated by hand, employing the principle of the lever or the screw, or by other means. Its action depends on the undiminished transmission of pressure through a liquid such as water or oil.

Hydraulic presses are expensive but highly efficient. The following principles are involved in their use: (1) Pressure

[1] Other presses are described by A. Goris and A. Liot, "Pharmacie galénique," Masson et Cie, Paris, 1939, Vol. 1, p. 634.

exerted at the surface of a liquid is transmitted equally in all directions and acts at right angles to all surfaces in contact with the liquid under pressure (Pascal's law). (2) The only force that can exist between a liquid at rest and the walls of the container is at right angles to the walls. (3) The final force exerted by the press is directly proportional to the area of the cross sections of the pistons.

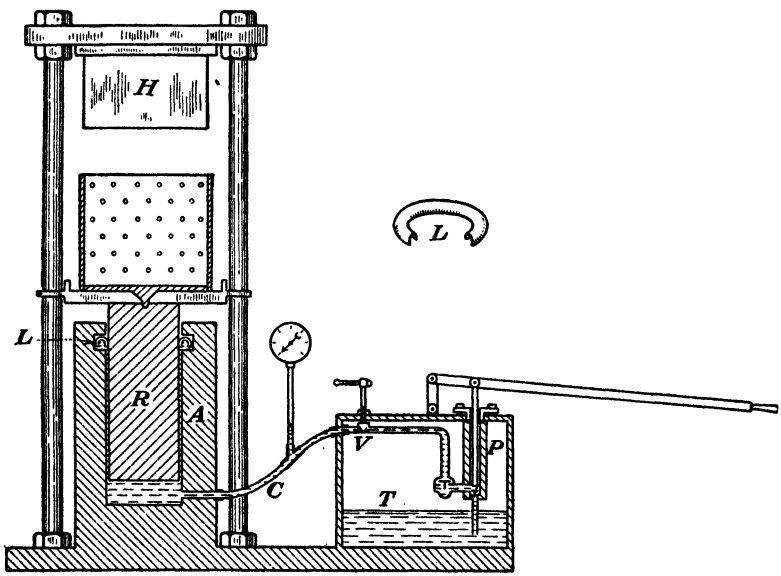


FIG. 132.—Section of a hydraulic press.

Example: Suppose at A a force of 100 lb. was applied, how much pressure would be exerted at C? (See Fig. 133.)

The force at B is calculated as follows: $2:16::100:x$.

$$2x = 1{,}600;\ x = 800 \text{ lb.}$$

The force at C is calculated as follows: $8:40::800:x$.

$$8x = 32{,}000;\ x = 4{,}000 \text{ lb.}$$

If used, the bags containing the material to be pressed should be strong, durable, and easily cleaned. They may be made of heavy canvas or horsehair cloth. Modern presses are made of various materials such as iron, enamelware (queen's ware or graniteware), wood, and porcelain. They may be heated by hot water or

steam. The nature of the liquid being removed determines the type of press to be used; for example, wooden presses should be used for acid liquids.

In using presses, moving parts should be well lubricated; pressure should be applied gradually and steadily to avoid injury to the bag holding the material or to the machine itself. Surplus liquid should be allowed to drain off or should be removed by being pressed lightly between the plates. For expression at high pressures, the bags or sacks holding the mixture should be made of cloth that is durable but not too thick.

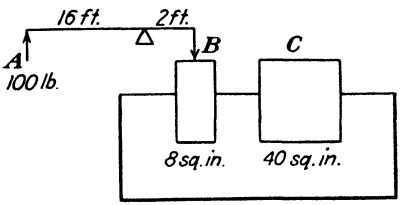


FIG. 133.—Diagrammatic sketch of a hydraulic press.

LOTION

Lotion (Latin *lotio* from *lavare, lotum,* to wash) is a process of purification by which soluble impurities are removed from insoluble matter—generally precipitates or magmas such as Magma of Magnesia U.S.P. XII and Magma of Bismuth N.F. VII—by the addition of small or large amounts of a suitable washing liquid. Its main purpose is to obtain the insoluble magma.

Historical.—As an English word, lotion has rarely been used to designate a process in pharmacy. In 1599, Gabehlouer used it in his "Book Physicke" to mean a washing of the body. The first use of the word in English was in 1549, when Latimer wrote in his Sixth Sermon before Edward, "Their doctrines were unsavory, it was but of lotions of cedimation . . . and such." In a British encyclopedia of 1797, lotion was described as a "washing as concerns beautifying the skin."[1]

Lotion may be of several types, **simple,** or **discontinuous,** usually for small amounts of precipitates; and **continuous washing,** accomplished by special assemblies or by decantation and in commercial work by the use of filter presses.

[1] MURRAY. *Op. cit.*, Vol. 6, Part 1, p. 456.

Lotion may be accomplished by the use of hot liquids. However, this is generally done by the discontinuous method.

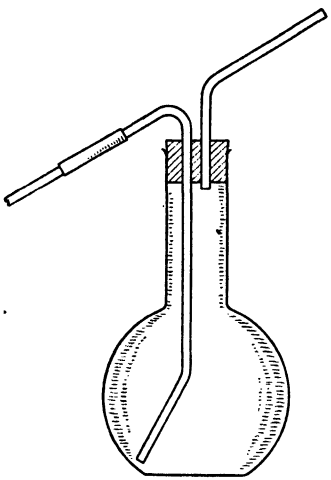


FIG. 134.—Continuous-flowing wash bottle.

Various official products are obtained by lotion as one of the processes involved, such as precipitated calcium carbonate, washed sulfur, tribasic calcium phosphate, and tribasic magnesium phosphate.

A process closely related to lotion is the metallurgical process of **lixiviation** (Latin *lix*, ashes, *lye*) by which many minerals can be washed of their soluble impurities by water (see also page 423). Lixiviation was practiced by the ancient Egyptians and Hebrews, who were skilled in the art of metallurgy. In early America, wood ashes were washed of their salts by lixiviation to furnish lye in making soap.

The apparatus for simple, or discontinuous, lotion in the laboratory consists of a funnel provided with a filter of paper,

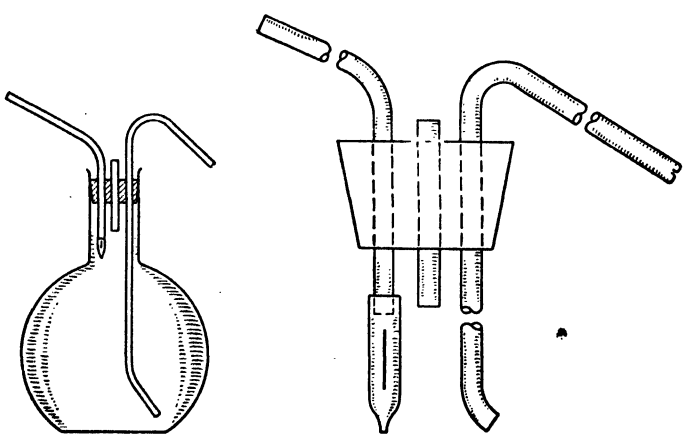


FIG. 135.—Automatic wash bottle.

cotton, or some other material to retain the solid matter or precipitate that is mixed with the washing liquid or through

which the latter passes bearing certain impurities in solution. This process is continued until the wash liquids show no more of the soluble impurities. This point may be determined by suitable qualitative tests as well as physical ones, such as absence of odor, color and taste, reaction to litmus, etc.

If small amounts of precipitates are to be washed on a filter paper, the latter should be underlaid with a piece of gauze to prevent tearing of the paper when it is taken from the funnel. The wash liquid is dispersed in a fine stream upon the solid

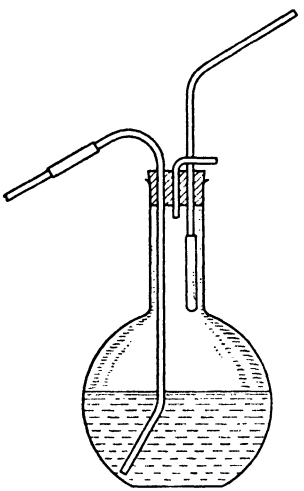


FIG. 136.—Spritz wash bottle.

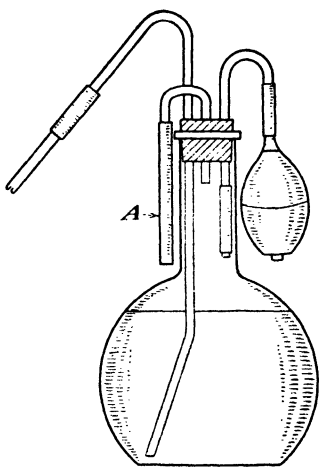


FIG. 137.—Handy wash bottle.

from the capillary tube of a **Spritz wash bottle,** of which there are several modifications, such as those of Amthor (Fig. 135),[1] Effinger (Fig. 134),[2] and Herman (Fig. 137),[3] which are of the **continuous-flowing type,** and those designed by Serinis (Fig. 138),[4] which are **nonsplash types.**

Lotion may be accomplished most readily by the use of small quantities of wash liquid well distributed from a wash bottle. Allowance must be made for complete drainage before using fresh liquid.

[1] FRANK AMTHOR. *Chemist-Analyst* **17** (No. 1), 18 (1928).
[2] B. T. EFFINGER. *Chemist-Analyst* **18** (No. 6), 21 (1929).
[3] E. H. HERMAN. *Chemist-Analyst* **20** (No. 3), 21 (1931).
[4] N. S. SERINIS. *Chemist-Analyst* **17** (No. 1), 15–16 (1928).

The precipitates, after washing, are freed from final traces of moisture by being pressed between weighted plates or in presses. In commercial work the centrifuge or a filter press is used.

Continuous Lotion.—There are several ways to accomplish continuous lotion, (1) by various types of continuous washing assembly, (2) by decantation, (3) by siphoning, (4) by pipetting, and (5) by dialysis. A number of forms of apparatus have been suggested by which large amounts of wash liquid may be added uninterruptedly until complete washing is ensured. Space does not permit a description of all these forms. Two that have been found satisfactory are shown in the accompanying figures.

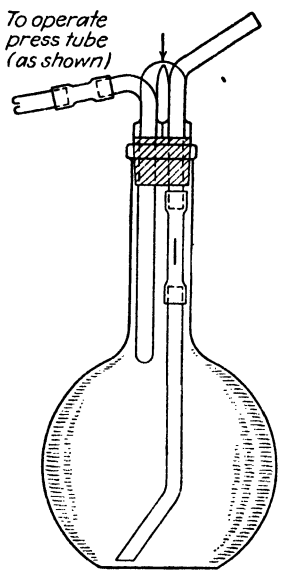


FIG. 138.—Nonsplash wash bottle.

Lotion by Decantation.—Decantation (Latin *de*, from, + *canthus*, the lip of a vessel) is a washing process involving the separation of a liquid from a subsided solid by carefully pouring off the supernatant liquid or by some other means of separation. It is especially valuable when large amounts of precipitates are to be washed repeatedly in order to remove impurities and also in washing gelatinous or similar products, such as magmas, which are difficult to filter but will settle out fairly rapidly.

Historical.—Lotion by decantation was used by the alchemists of Roman times. The term was first used in English by the Irish chemist Robert Boyle in his "Original Forms and Qualities" in the phrase "having carefully decanted the solution into a conveniently sized retort." In 1641, in a French publication on distillation, the process was described as "the pouring off of any liquor which hath a settling by inclination."[1]

Decantation is applicable in the laboratory for washing small amounts of precipitates and when comparatively small amounts of the wash liquid are used at a time. The material to be washed is placed in a precipitation vessel, an ordinary beaker, or some

[1] MURRAY. *Op. cit.*, Vol. 3, Part 1, pp. 85–86.

other suitable vessel with perpendicular sides. The wash liquid is added, this action being accompanied by continuous

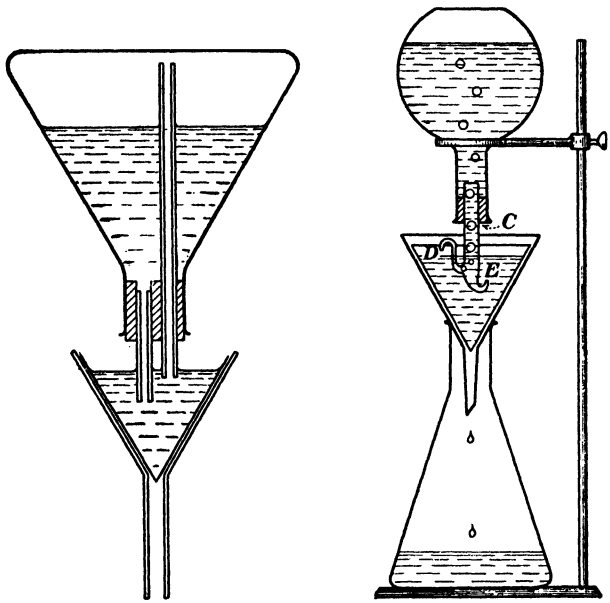


FIG. 139.—Types of continuous washing apparatus.

stirring with a glass rod. Settling is allowed to occur. Then, with as little agitation as possible, the supernatant liquor is

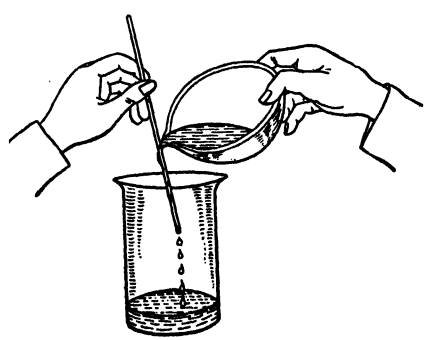


FIG. 140.—Simple decantation.

poured off, a guiding rod (Fig. 140) being used as an aid. This process is repeated until suitable tests show that all the impurities

have been removed. The precipitated material is then collected, depending on the amount, on a smooth filter, a straining cloth or bag, or in some other manner. The success and speed of this operation depend (1) on the shape and size of the vessel from

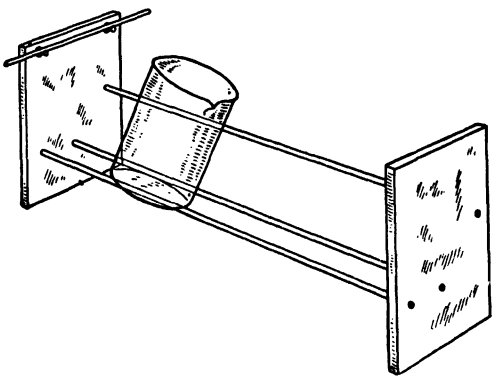


FIG. 141.—Design for a decantation rack.

which the liquid is poured, (2) on the nature of the liquid being removed, and (3) on the amount of liquid being poured off, since the more complete the removal of the supernatant liquid the more efficient the washing.

Moody[1] has designed a convenient and simple rack to hold beakers, to allow for the settling of precipitates prior to decantation. If settling is not complete, the liquid should be passed through a filter in order to prevent loss of the precipitate, especially if it is desired to preserve the latter. It is advisable to pour from the side of the container opposite that bearing the label. If a guiding rod is not used, a thin film of oil or oily substance such as tallow, lard, or rosin cerate may help prevent the stream from running down the side of the vessel (Fig. 141).

The siphon and its use are generally familiar in the laboratory and elsewhere. If properly accomplished, siphoning is a convenient method of transferring a liquid from one level to another, with a minimum loss. In its simplest form the siphon is a U tube with one arm longer than the other. The tube is first filled and then immersed so that the short arm dips into the liquid to be removed. The siphon may also be started by applying suction at Y (see Fig. 142). Distance BY is greater than AX, the flow of the liquid is from A to Y, and the speed is equivalent to a force proportional to the difference between AX and BY.

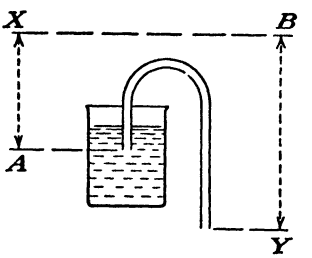


FIG. 142.—Design of a simple siphon.

Siphons may also be of the automatic type for transferring acids, alkalies, and other irritating liquids (see Fig. 143).

Lotion by the Use of Pipettes.—This form of lotion may be resorted to if *small* quantities of precipitates are to be washed by *small* amounts of wash liquids. It may be accomplished by pipettes similar to transfer pipettes or by means of medicine droppers.

Theoretical Considerations of Lotion.—Marsh[2] proposes the following formula for calculation of lotion by decantation: $C_n = (V_1/V_0)^n C_0$ where C_0 is the initial concentration of impurity removed by decantation, C_n is its concentration after the nth washing, V_0 equals the volume of the vessel in which the washings are carried out, and V_1 is the volume of the settled precipitate. It can readily be seen that, the greater the ratio of the volume

[1] A. H. MOODY. *Chemist-Analyst* **17** (No. 1), 19 (1928).
[2] G. EVERETT MARSH. *Ind. Eng. Chem.* **20**, 1241 (1928).

of the supernatant liquid to the volume of the precipitate, the fewer the number of washings required. When the volume of the precipitate is one-tenth the total volume V_0, 4 washings will accomplish as much as 6 washings when the volume of the precipitate is twice as large and as much as 10 washings when the precipitate is four times as large. The volume of the wash water is $4 \times 0.9 = 3.6$ volumes; in the second washing, the volume is $6 \times 0.8 = 4.8$ volumes; in the third washing, it is $10 \times 0.6 = 6$ volumes.

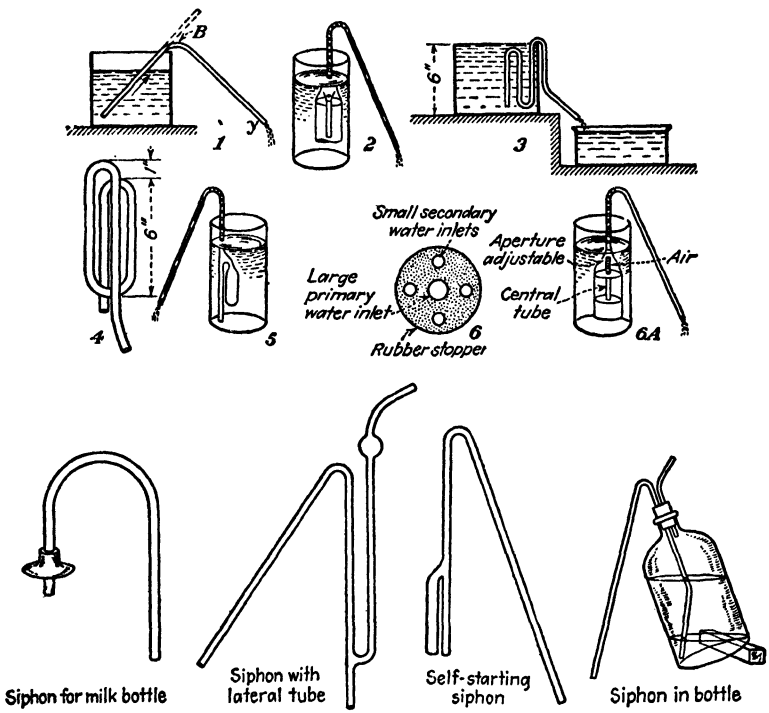


FIG. 143.—Types of siphons.

Examples: In a given vessel the precipitate occupies 0.4 of the volume of the vessel. The impurities are 25 Gm. per L. After 5, 8, and 10 washings, what are the respective amounts of impurities? After 5 washings there will be 0.01 of 25 Gm., or 0.25 Gm. per L.; after 8 washings, 0.00065 of 25 Gm., or 0.016 Gm. per L.; after 10 washings, 0.0001 of 25 Gm., or 0.0025 Gm. per L.

How much wash water will be required to reduce the concentration of the impurities to 0.001 Gm. when the volume of the precipitate is 0.5 that of the vessel? Referring to Fig. 144, it is observed to be 5 volumes, *i.e.*, $5V_0$.

Continuous Lotion by Dialysis.—Insoluble solids are sometimes of such a character as to be difficult to rid of soluble

impurities by the usual methods. In such cases **dialysis** (see Chap. XIII, page 396) may be used.

In 1936, Moness, Lott, and Christiansen[1] proposed washing milk of magnesia (Magma Magnesiae U.S.P. XII) by means

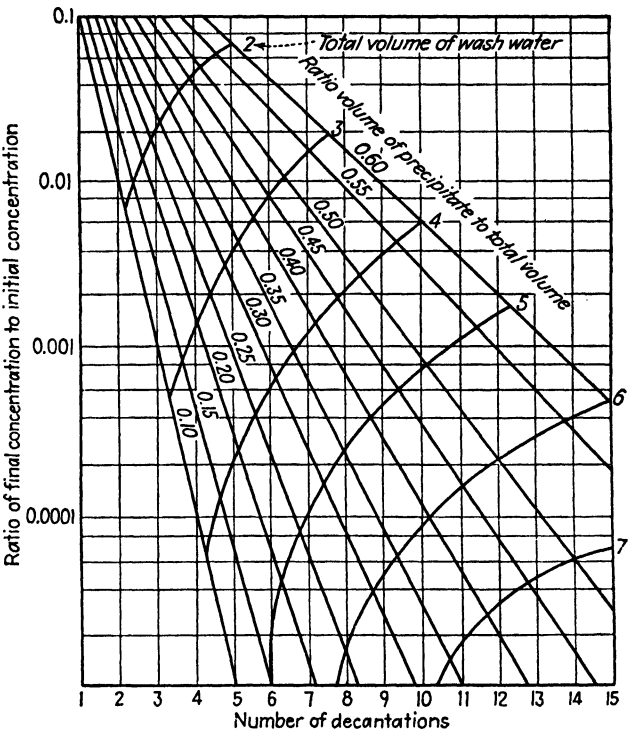


FIG. 144.—Marsh's graph for estimating volumes of wash liquid in lotion.

of large-scale dialysis. This particular preparation has the distinct disadvantage when washed by the decantation method that the rate of settling is slow, even when the temperature is well above that of the room.

FILTRATION

Of the strictly mechanical processes, none is more important to the practice of pharmacy than **filtration,** and yet none is so

[1] E. MONESS, W. A. LOTT, and W. G. CHRISTIANSEN. *J. Am. Pharm. Assoc.* **25,** 524–9 (1936).

generally inefficiently employed. A pharmacist should never dispense or sell a preparation that is a solution unless it is brilliantly clear in appearance. In most cases this property can readily be obtained by **filtration under proper care and conditions.**

Filtration (Italian *filtrare*, to filter or strain; from Latin *filtrum* or *feltrum*, felt) is the separation of solid particles from liquids, with the simultaneous clarification of the latter by the use of the funnel and filter paper or other **septa.** More broadly, filtration may be defined as the alteration of the composition of a stream with the aid of an apparatus (liquids, light, and radiation).[1] When applied to liquids and solids it involves a porous layer—**the filter or filtering medium**—the liquid passing through—**the filtrate**—and the insoluble matter—**the precipitate** (sediment)—that is deposited at the surface of the septum. The process differs from **colation** (straining) in that it brings about a more complete separation of the insoluble matter because the porous medium used is of much finer texture.

Historical.—Filtration is a very old process, and there is no clear evidence as to when it first came into use. It was first described as a chemical process by Geber, the famous Arabian alchemist, who distinguished it as a means of distillation without heat and that he called *destillato per filtrum.* This expression was invariably used in the Middle Ages to describe **anethisis,** a straining-off process, while the word *filtratio* was used for ordinary filtration as we think of it today. Because of the confusion of terms it is possible that the first use of the term filtration applied to anethisis. Plato makes reference to a purification process by which a liquid is transferred from one container to another by the capillary action of fibers such as wool.[2]

Filtration Factors.—The object of filtration may be either the collection of a precipitate, in which case the filtrate may be rejected, or the clarification of a liquid where the solid is valueless. Factors influencing filtration may be deduced from the theory of the passage of a liquid through capillary tubes. The rate of flow of a liquid through a capillary is given by Poiseuille's law:

[1] A. L. Von Scherpenburg. *Tydschr. Algem. Tech. ver Beetwortsuckerfahr. Raffinsindeurs* **32,** 17–19 (1938); *Chem. Abstracts* **30,** 7914 (1936).

[2] Walter H. Blome and Charles H. Stocking. "Fundamentals of Pharmacy," Lea & Febiger, Philadelphia, 1939, pp. 98–99.

$$V = \frac{\pi R^4(P - p)}{8ln}$$

where V equals the rate of flow, R the radius of the capillary, l the length of the capillary, n the coefficient of viscosity of the liquid, P the pressure of the downward column of air, and p the pressure of the upward column of air. The value of P may be increased in small-scale operations in the conical filter funnel by increasing the surface exposed to the atmosphere or, as in the case of the filter press, by augmenting the atmospheric pressure behind or above the liquid. If, conversely, the value of p is lowered, the expression $P - p$ becomes greater and the value of V is correspondingly increased as in the case of suction or vacuum filtration; the rate of filtration varies inversely as the viscosity n. Glycerin solutions of high viscosity pass through a filter much more slowly than alcoholic liquids. The viscosity of a liquid, however, is much reduced by raising its temperature; and if filtration is carried out at a high temperature, at which the viscosity of the liquid is lowered, the rate of filtration can be greatly acccelerated. Mathematical accuracy in arriving at a value of V is not possible since some of the factors are not susceptible to exact evaluation. The rate of flow is affected by electrical charges, adsorption, etc.[1]

In the case of **simple filtration,** the **porous medium** most commonly used is unsized, pure, white paper of varying degrees of durability and texture depending on the purpose to which it is being put. **Filter paper** may be obtained in sheets or, more commonly, as disks, which are more convenient to use and fold. The paper to be used in gravimetric analysis, in processes where it is to be ignited with the precipitate, is known as **ashless filter paper,** and is specially treated to yield a small and known amount of ash upon ignition to constant weight.

Forms of filter media, or septa, in addition to paper, are paper pulp, cotton, linen, felt, sand, asbestos, ground glass, charcoal, porous stone, sintered glass, alundum, and screens of metal cloth (for filter presses) and metal wire of various types.

Methods of Folding Filter Papers.—Filter papers should be folded so that they will fit the funnel being used, will have

[1] *Chemist and Druggist* **132** (No. 3129), 71 (1940).

sufficient support to withstand the pressure or weight of the material they are supporting, and will permit as rapid filtration as possible. Numerous methods of folding papers have been recommended, only a few of which are discussed here.

1. First fold the disk in the middle (AB). Then bring A to an exact fit with B, and crease, open, and set in funnel (Fig. 145). It will be noted that such a filter has as one half of its surface one thickness of paper and as the other half three thicknesses. This is the quickest and most commonly used method of folding a paper; however, such a filter may not always fit the funnel closely.

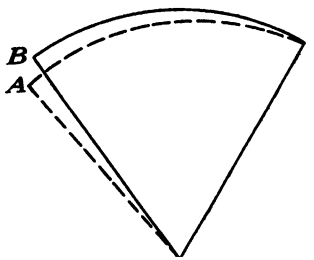


FIG. 145.—Most commonly used type of plain filter.

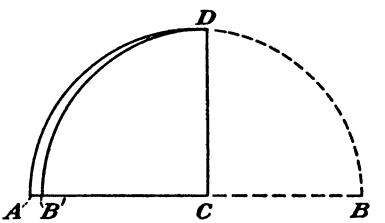


FIG. 146.

2. The fault may be partly obviated by folding the paper as in Fig. 146.[1] Fold the disk in the middle (AB); then, instead of bringing B directly to A, bring to B', which throws C slightly off center. No air will pass along $B'C$, and line $B'D$ is so long that no air will leak through.

3. The following procedure for folding is of practical value if the funnel does not have an angle of exactly 60 deg. A represents the size to which the paper is folded to fit most funnels. The corner C is torn off so that when the paper is placed in the funnel the crease B cannot draw air, which lessens the rate of filtration. Good contact between the paper and funnel is shown at 1. The absence of a fold of paper extending to the top of the filter prevents air from being drawn down the side of the funnel at 2. The point of the filter is centered over the outlet but not touching the sides of the funnel at 3 (Fig. 147).[2]

[1] A. REGENBRECHT. *Chemist-Analyst* No. 39 (June, 1923), p. 21.
[2] H. A. NOYES. *Chemist-Analyst* No. 23 (February, 1918), p. 18.

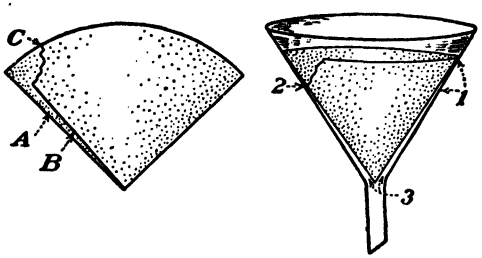


FIG. 147.

4. Another form is a type of plaited paper. The ordinary filter has the disadvantage that one half is of triple thickness and the other half of single thickness; it thus tends to pull in air and give an uneven flow. In 1*a* the paper, after being folded into halves, is folded into thirds and then into halves again (1*b*).

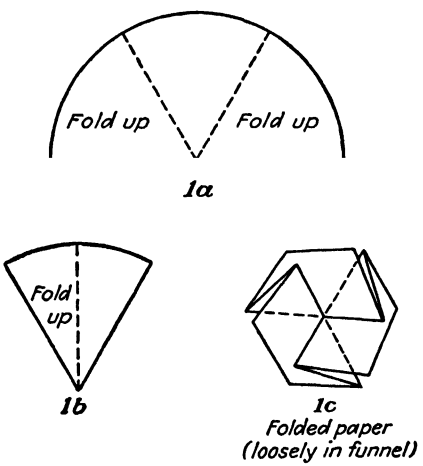


FIG. 148.

The paper is opened and with a little guidance is caused to take the form shown in 1*c*. The triple and single thicknesses are now arranged symmetrically around the funnel, bringing about a more even distribution of the solid and more rapid filtration (Fig. 148).[1]

5. The following method has been found to be unusually satisfactory, primarily because it distributes the paper more

[1] LESTER MEYER. *Chemist-Analyst* **21** (No. 4), 18 (1932).

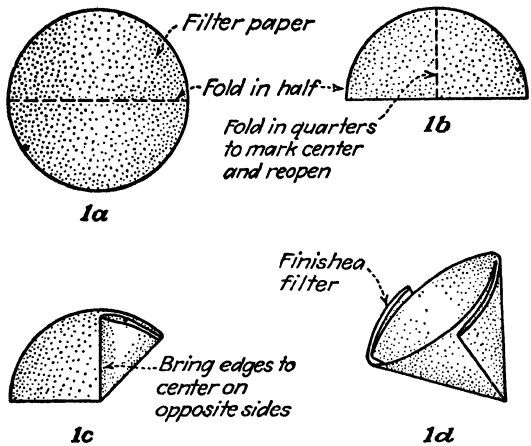
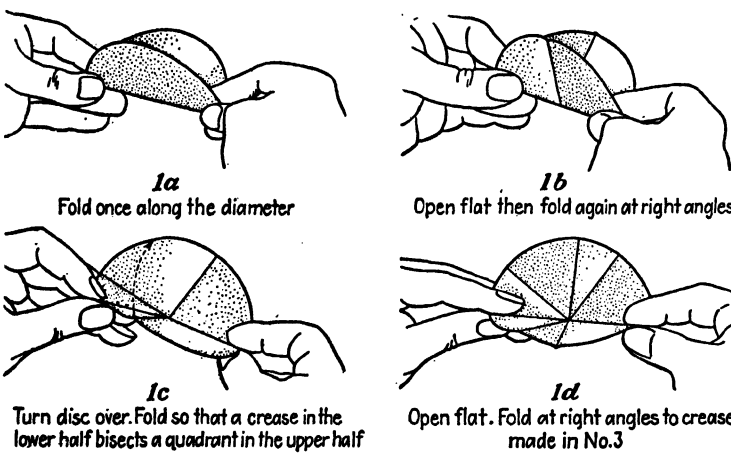


FIG. 149.



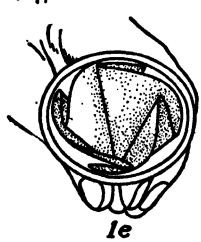


FIG. 150.

uniformly (Fig. 149): The paper is folded in half (1*a*) and then into quarters (1*b*). Reopen and bring the edges to the center

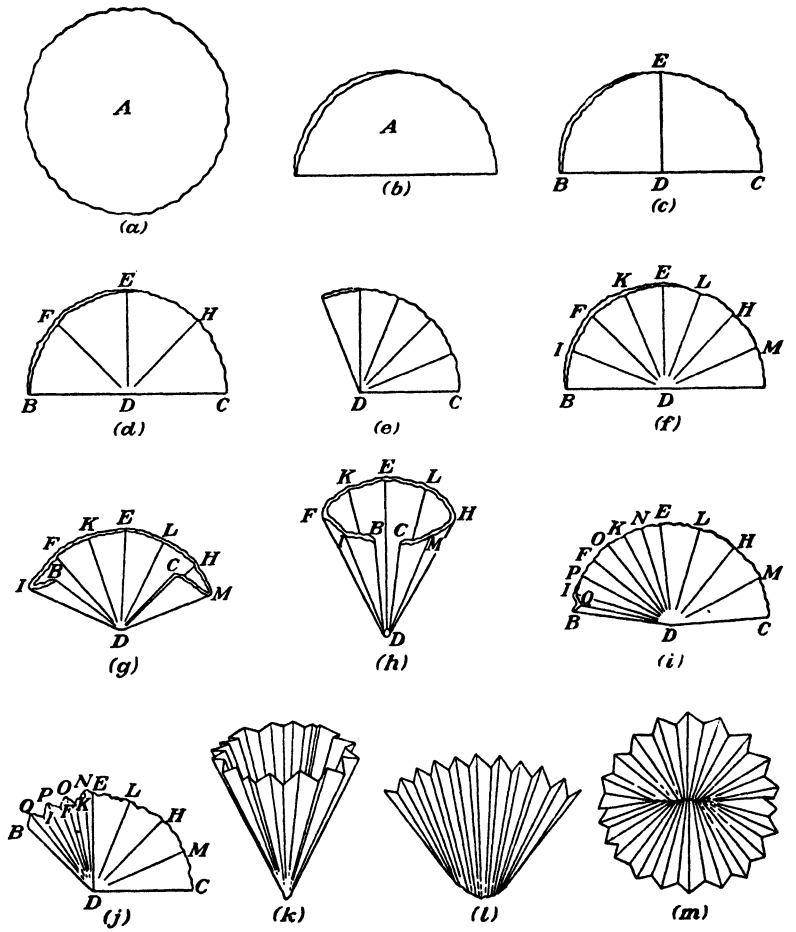
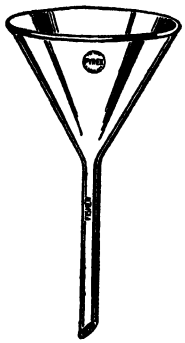


FIG. 151.—The plaited filter paper.

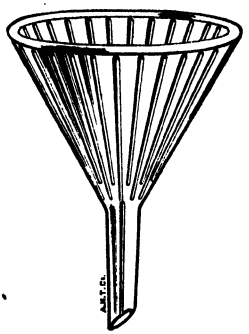
on opposite sides (1*c*). The filter, ready for the funnel, is shown in (1*d*).[1]

6. A quadruple fold of the filter has been used with marked success in ordinary filtration and in filtrations involving quanti-

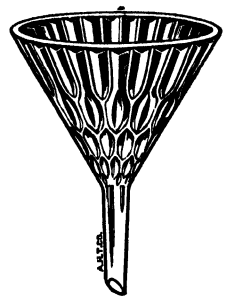
[1] CHARLES A. SCOGLAND. *Everyday Science and Mechanics*, 6 (No. 6, December), 971 (1935).



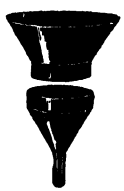
Short-stem funnel.



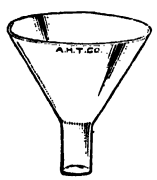
Ribbed funnel.



Fluted funnel.

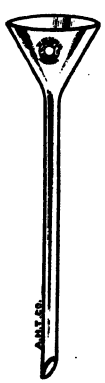


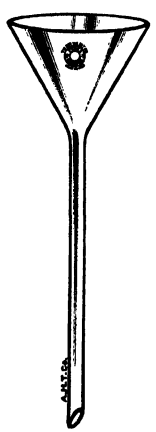
Rubber straining and powder funnel.

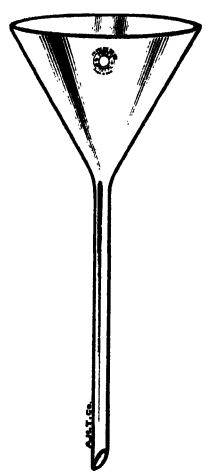


Funnel for transferring powders.

Metal funnel for transferring liquids.







Long-stem funnels.
FIG. 152.

tative technique. Such a filter acts more rapidly than most.[1] The method of folding is shown in Fig. 150.

7. The **plaited filter** (also called pharmacist's filter or pleated filter) is a multifold filter that has been in general use in simple filtrations of larger quantities of liquid in the pharmacist's laboratory and where a large filter may be used to advantage. Nevertheless, the advantages and efficiency of this type of filter are open to question. It has been found that the quadruple-fold filter described under (6) is equally serviceable and efficient for small and large volumes of liquid mixtures.

Paper for the plaited filter is available on the market already folded; to fold it properly and quickly in the laboratory requires practice. One precaution must always be observed in folding: the creases should never be brought to the tip of the cone, for thus the apex of the filter is weakened and the paper will tear easily at this point when a considerable quantity of liquid is put in. Figure 151 shows steps to be followed in folding such a filter.

Funnels.—In simple filtrations the filtering medium is supported in a device known as the funnel, which is a conical-shaped instrument of glass or metal. The funnel also facilitates the pouring of liquids from one vessel to another, especially if the vessels have narrow openings, and certain funnels are used to transfer powders. Figure 152 shows the several types.

Funnels may be made of glass, bakelite, hard rubber, porcelain, graniteware, earthenware, copper, tinned copper and iron, and galvanized iron. **Metal funnels** are durable and easy to clean but are subject to attack by chemicals and have little use at the prescription counter. They are of value in filtering large quantities of noncorrosive liquids as well as in transferring them. **Funnels of enamel-, granite-, or agate-ware** have a tendency to chip easily. Some metal funnels are provided with valves for transferring liquids in the funnel.

Glass funnels are the ones most commonly used by the pharmacist for small-scale work, especially at the prescription counter. They should be made with an angle of exactly 60 deg. to ensure proper fitting of the filter paper. This type of funnel is transparent and easily cleaned but is more likely to break.

[1] *The Laboratory*, Fisher Scientific Co.

Hard-rubber funnels are not generally used since they are comparatively expensive, not transparent, have a tendency to warp, and become brittle when used with hot liquids. **Porcelain** and **earthenware funnels,** while not transparent, are sturdy and easily cleaned but are more expensive than glass.

Funnels are generally held in stands called **funnel supports** or **funnel stands,** which are usually made of wood (Fig. 153). The use of iron rings on iron supports should be avoided as they are often rusty and the rust is apt to rub loose and fall into the filtrate.

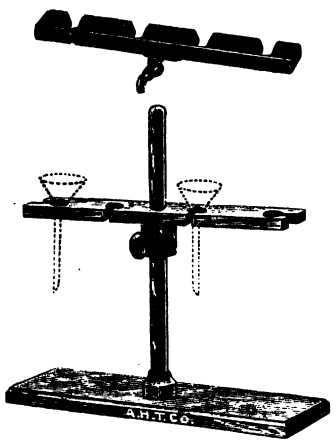


FIG. 153.—Funnel supports.

Aids to Filtration.—The **filter aids** might be considered as filtering media in that, by mechanical absorption or, in some cases, by adsorption, they will remove solid and liquid particles in such a fine state of subdivision that they will pass through the pores of ordinary filter paper. The substances generally used are powders in a fine condition (see the discussion of decoloration, clarification, and deodorization, pages 514, 515, and 519). They should be insoluble and inert and should be used with caution and proper selection so that, by adsorption, active agents will not be removed from the solution along with the undesirable solid material. In using a filter aid the rate of filtration increases with (1) the percentage of filter aid used, (2) the filtration temperature, (3) the filtration pressure, (4) the dilution of the liquid, and (5) the fluidity of the liquid.[1]

The following substances are used as aids to filtration:

Paper pulp is especially effective, acting by mechanical absorption. It is prepared by stirring shredded filter paper with cold distilled water, adding boiling water, agitating by means of a spatula or stirrer until disintegrated, and then pouring onto a straining cloth or filter.

[1] A. O. ROBSON. *J. Proc. Sydney Tech. Coll. Chem. Soc.* **7**, 31–40 (1935–1937); *Chem. Abstracts* **34**, 7661 (1940).

Purified Talc U.S.P. XII is stated to be nonadsorbent but is absorbent. It is used for the preparation of waters, spirits, and elixirs. It has one disadvantage in that it is too finely divided and tends to run through the filter paper. If this occurs, the filtrate should be returned to the funnel until the pores of the paper have become closed. This sometimes requires considerable time. A mixture of equal parts of talc and pulverized asbestos in the tip of the filter has been recommended.

Purified Silicious Earth U.S.P. XII (infusorial earth, diatomaceous earth, or diatomite) is used as a nonadsorbent and efficient aid. **Clays,** such as fuller's earth, kaolin, and bentonite, may be used, but some have the disadvantage of adsorbing coloring matter and alkaloids.

Wood and **animal charcoals** are especially effective but have unusual selective adsorptive properties (see Decoloration, page 514).

Chalk, precipitated chalk, magnesite, magnesium oxides and carbonates, and calcium and magnesium phosphates have also been used. However, these are not suited for acid solutions, and some may also give undesirable reactions to the filtrate and cause incompatibilities in prescriptions.

Silica gel, aluminum oxide (alumina), filter cel, and asbestos have been used to advantage.

Krantz and Carr,[1] in filtration experiments, have made a study of filter aids and report that the clarification of Aromatic Elixir U.S.P. XII is the result of the coagulation by neutralization of the charges on the oil particles in the elixir by oppositely charged ions in the solution and absorption of the coagulated particles by an insoluble filtering agent exhibiting an immense surface. Table XXV gives the results that these workers obtained with some filter aids.

These results indicate that precipitated magnesium carbonate is the most effective filter aid. Magnesite is scluble (10 mg. per 100 cc.) and is primarily a coagulant; the solubility of talc is negligible, and its use as a filtering agent depends almost entirely on its absorptive capacity. Precipitated magnesium carbonate is soluble to the extent of 40 mg. per 100 cc. and

[1] JOHN C. KRANTZ and C. J. CARR. *J. Am. Pharm. Assoc.* **19,** 1095 (1930); **20,** 784 (1931).

because of its bulky nature exhibits a tremendous surface acting as a coagulant as well as an absorbent. The efficiency of talc

TABLE XXV

Filter aid, 3 Gm. per 100 cc.	Number of filtrations required for clarification	Turbidity, parts per million
Sodium chloride	5	3
Fuller's earth No. 200	2	4
Magnesite No. 60	2	2
Magnesite No. 100	4	3
Precipitated magnesium carbonate	1	1
Magnesium oxide	1	1
Magnesium chloride	4	0.5
Talc No. 100	2	2
Alum	..	0.5

is augmented by the addition of small amounts of electrolyte such as sodium chloride. The chief objection to the use of magnesium carbonate is its alkalinity. For this reason, magnesite is recommended.

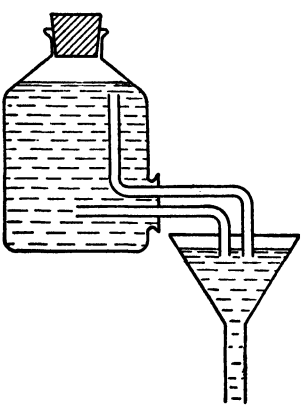


FIG. 154.—Automatic filter replenisher

Continuous Filtration.—A filtration assembly may be of the **continuous,** or **automatic,** type similar to the continuous washing assembly (page 475), the filtration assembly shown in Fig. 154,[1] or the constant-flow type shown in Fig. 155.[2] In filtering, it is essential for the stem of the funnel to remain constantly full and for the flow from it to be continuous and uninterrupted; this necessitates accurate and close fitting of the paper to the funnel to avoid pulling in air. Davis claims that the following modifications usually recommended to augment filtration have been proved futile: (1) notching the paper at the edge (see Fig. 147), (2) having the stem of minute bore and the

[1] JAMES CAREY. *Pharm. J.* **148,** 42 (1942).

[2] CHARLES B. DAVIS. *Chemist-Analyst* No. 49 (February–March), p. 13.

point ground to a 60-deg. angle, (3) constricting the stem of the funnel at the vertex of the cone (Fig. 156), (4) having the cone ribbed and channeled in various ways (Fig. 152), (5) constructing

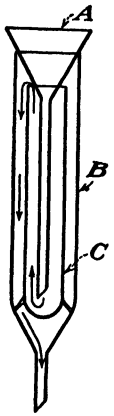


FIG. 155.—Constant-flow filtration assembly.

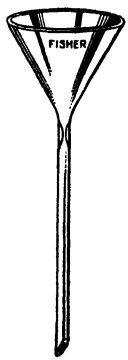


FIG. 156.—Funnel with constricted stem.

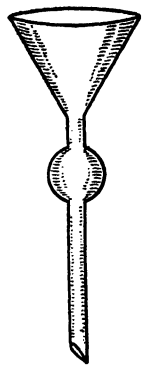


FIG. 157.—Funnel with bulb in stem.

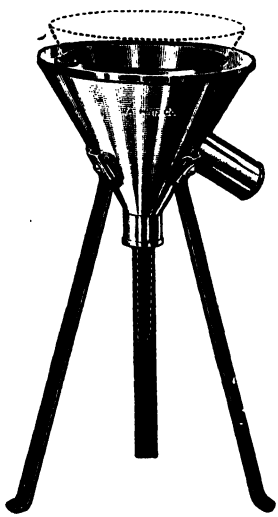


FIG. 158.—Hot-water funnel.

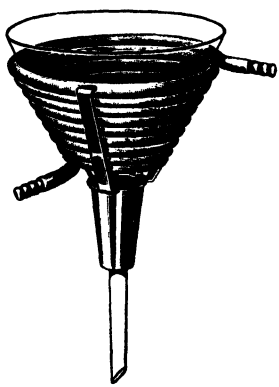


FIG. 159.—Spiral hot-water funnel.

a bulb in the stem (Fig. 157), (6) plaiting the filter paper. In Davis's assembly, the funnel *A* rests on the outer tube *B*, and its stem reaches to the bottom tube *C*, which may be unattached

or sealed to *B* or held by a rubber adjunct. A Büchner or sugar funnel with a Gooch crucible and rubber ring may be substituted for the ordinary funnel. This funnel may serve for double filtration by lining the cone of the funnel with filter paper and embedding the stem in sand, fuller's earth, filter cel, activated

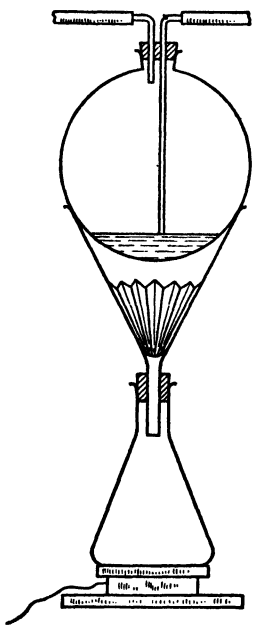


FIG. 160.—Hot extraction and filtration apparatus.

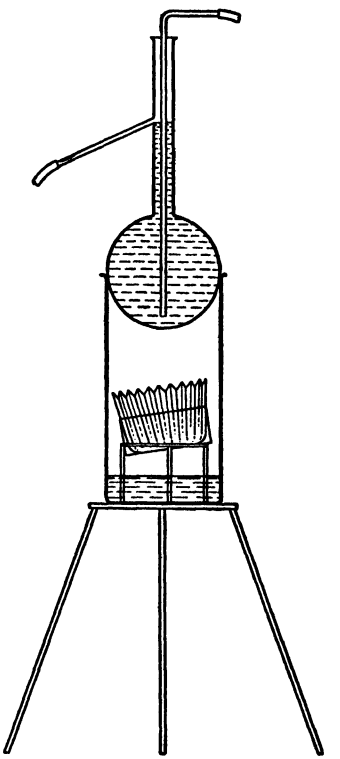


FIG. 161.—Tanner's apparatus for hot extraction.

carbon, or a solvent such as carbon tetrachloride. These continuous filtration assemblies may be used to conduct washings.

Hot Filtration.—In pharmacy, it often becomes necessary to remove solid impurities from gelatin, jellies, agar jellies, white and yellow waxes, petrolatum, cerates, ointments and other salvelike preparations, benzoinated lard, suet, etc. To do this the filter should be maintained at a temperature that will keep these products in a liquid state as the filtration proceeds. This

may be accomplished (1) by the use of a **hot-water funnel** (Fig. 158); (2) if steam or hot water is available, by means

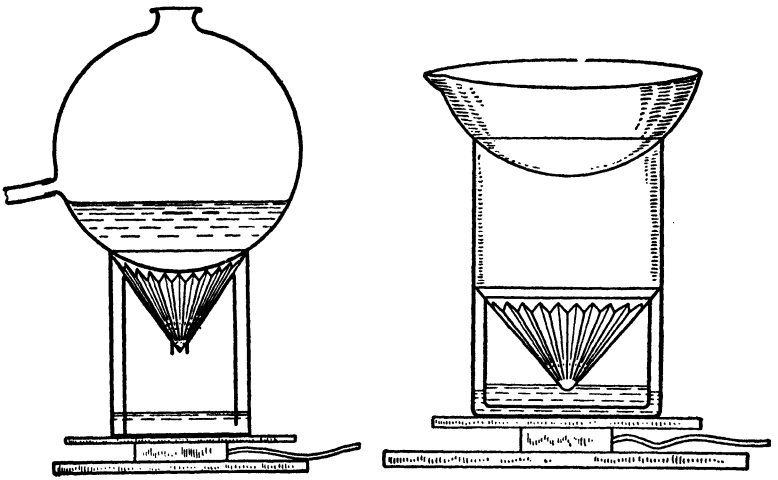


FIG. 162.—Assemblies for simple hot filtrations and crystallization.

of coils about the funnel (Fig. 159); (3) by placing the filtering apparatus in an air oven maintained at a desired temperature; (4) by an apparatus shown in Fig. 160;[1] (5) by Tanner's apparatus (Fig. 161);[2] and (6) by the assemblies recently proposed by Dawson and Dehn[3] (Fig. 162).

Acceleration of filtration is accomplished in the following ways: (1) by plaiting the filter paper; (2) by using a ribbed or fluted funnel; (3) by a combination of (1) and (2); (4) by lengthening the funnel stem by means of a loop in the stem (Fig. 163); (5) by making a constriction in the funnel stem; (6) by suction, or vacuum, filtration; (7) by increasing the pressure on the

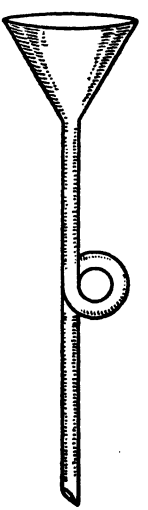


FIG. 163.—Funnel with loop in stem.

[1] J. B. CONANT. "Organic Synthesis," John Wiley & Sons, Inc., New York, 1922, Vol. 2, p. 49.

[2] H. G. TANNER. *Ind. Eng. Chem. Anal. Ed.* **4**, 397 (1932).

[3] JOHN W. DAWSON and W. M. DEHN. *Ind. Eng. Chem. Anal. Ed.* **12**, 317 (1940).

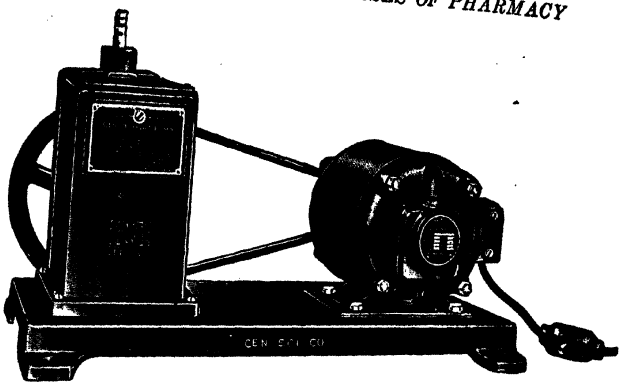


FIG. 164.—High-vacuum pump.

liquid to be filtered. Methods 1 to 5 have been discussed to some extent earlier in this chapter. Their expected efficiency may be subject to question, as much depends upon the skill of the operator.

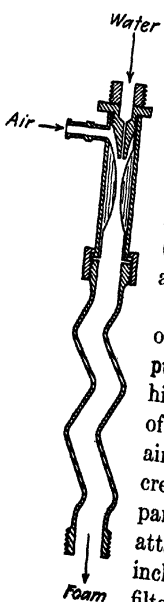


FIG. 165.—Richard's filter pump.

Suction Filtration.—This form of filtration is a satisfactory laboratory procedure for accelerating the process. The suction beneath the filter may be developed by means of **filter pumps** (aspirators) or vacuum pumps (Fig. 164). (See also Fig. 83.)

Filter pumps are obtainable in various forms, one of the most satisfactory being the **Richard's pump** (Fig. 165). Through a fine jet and at a high rate of speed, tap water flows in at the top of the pump and down the vertical tube, pulling air through the side arm of the tube and thus creating a partial vacuum in any closed or partly closed system to which the side arm is attached. Accompanying pieces of equipment include a water trap, a filter flask, funnels, filtering media, and, if the measurement of the reduced pressure is desired, a manometer (see Fig. 166).

The **water trap,** while not essential, is a safety device that should **always** be used if the filtrate is to be recovered, to avoid its dilution with water, which is brought about by the backward

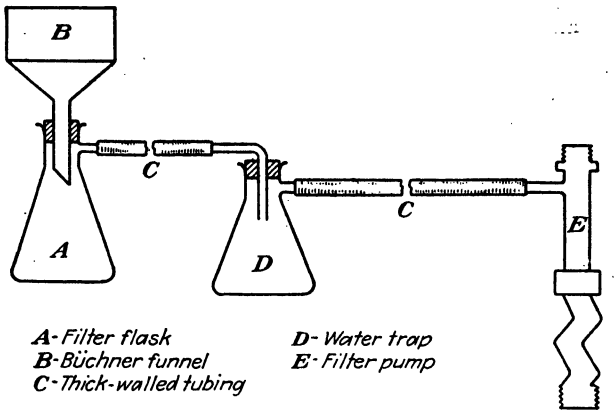


FIG. 166.—Assembly for suction filtration.

flow of the water through the side arm of the filter pump. This frequently occurs in the laboratory where a number of workers are apt to bring about a sudden variation in the pressure of the

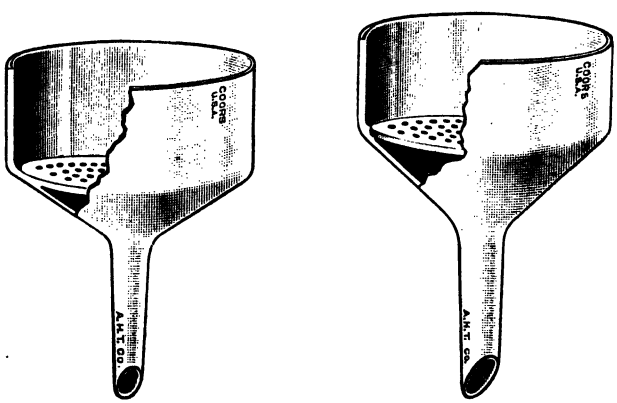


FIG. 167.—Büchner funnels.

water in the water line. **Filter flasks** should be thick-walled vessels provided with a side tubulature for connection to the trap and to the pump. In making connections, a rubber tubing

with thick walls should be used. The most satisfactory funnel to be attached to the filter flask is the **Büchner funnel** (Fig. 167), which may be heated or cooled and which has a perforated bottom. Filtering media for this type of funnel may be

FIG. 168.—Sintered-glass crucible.

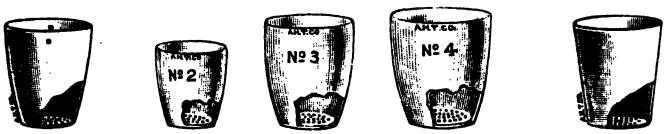


FIG. 169.—Gooch crucibles.

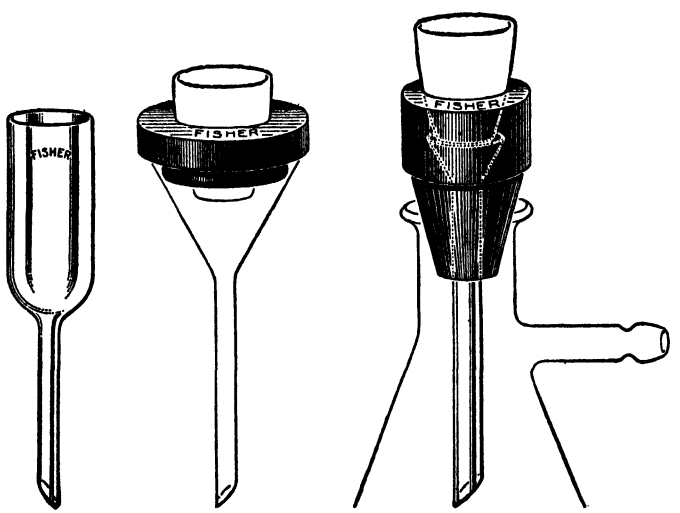


FIG. 170.—Crucible holders.

paper pulp, filter paper, cloth, or an asbestos mat. For filtrations involving the removal of small amounts of solid matter, especially in quantitative work, the Gooch porcelain crucible, alundum crucible, and sintered-glass crucible (Fig. 168) may be employed. The **Gooch crucible** (Fig. 169) is made of perforated

porcelain and has a bottom of porous glass with openings of various sizes. The alundum and sintered-glass crucibles have the disadvantage that they are difficult to clean. If crucibles are employed, it is necessary to use **holders,** of which several types are available (Fig. 170).

The ordinary funnel may be used in suction filtration if it is provided with a cone to hold the filter paper or with a porous cone (Fig. 171). Mumford[1] suggests a "repeating filter"

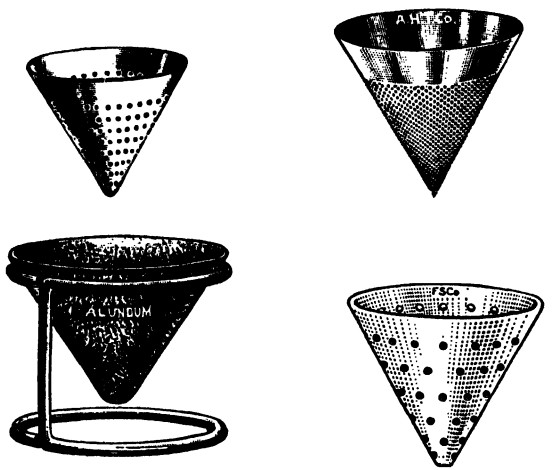


FIG. 171.—Filter cones.

contrived by using an ordinary funnel and a filter cone (Fig. 172). The cone is inverted in a short-stem funnel, and a small amount of asbestos fiber is used to seal the cone to the funnel. If large quantities or several small samples of the same material are to be filtered, the insoluble matter is collected by pouring the liquid on the tip of the cone. The precipitate is washed down onto the asbestos, and thus a fresh filtering surface is provided for each addition of the liquid to be filtered. It is claimed that 30 to 40 filtrations can be made without constructing a new filter.

Serinis[2] describes a rapid filter for quantitative filtrations that he asserts is a combination of some of the desirable features of the ordinary, the Gooch, and the Büchner funnels (Fig. 173). A thick asbestos mat *A* is prepared in

[1] KENNETH O. MUMFORD. *Chemist-Analyst* **21** (No. 5), 18 (1932).
[2] N. S. SERINIS. *Chemist-Analyst* **17** (No. 4), 17 (1928).

a Büchner funnel, a piece of filter paper *B* is placed over it, and *A* and *B* are washed with hot water until all loose particles are washed away, as is evidenced when the wash liquid is clear. The filter may be used with *A* only, especially when strong acids or alkalies, etc., would destroy filter paper, and may be used over and over for the same type of filtration. Disturbing the asbestos in pouring the liquid into the funnel may be avoided by placing a small piece of glass on *A* and directing the stream onto it. The filter may be used with *A* and *B* where *B* acts as a protection for *A*, especially in pouring and for filtrations of soluble precipitates.

After filtration, the main portion of the precipitate is removed with the filter paper, the residue in the funnel is washed away with solvent and hot

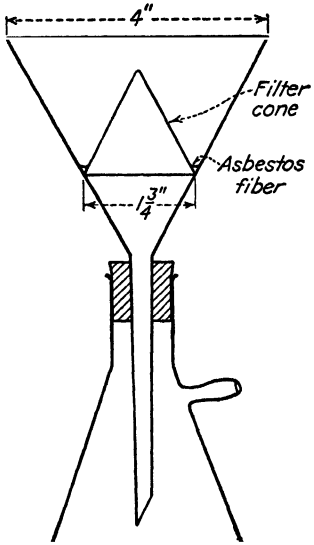


FIG. 172.—Repeating filter.

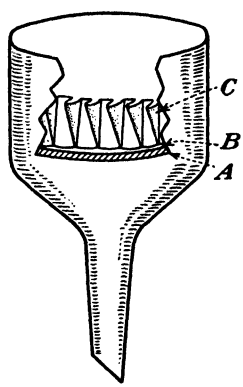


FIG. 173.—Rapid filter.

water and another filter paper placed on *A*, and the assembly is ready for another filtration. This filter is said to be faster than the ordinary Büchner funnel: the filter paper will not break under high suction, fine precipitates difficult to filter can be removed quickly and completely, and the time of filtration and the washing of precipitates is thus reduced. The filter may be used as *A*, *B*, and *C* for combined filtration of insoluble precipitates, which must be removed in some other way than by solution; *C* is folded as shown in Fig. 173. For regular laboratory work, the 55- and 125-mm. Büchner funnels are satisfactory.

Another form of suction-filtration apparatus is the **filter leaf** (Fig. 174).

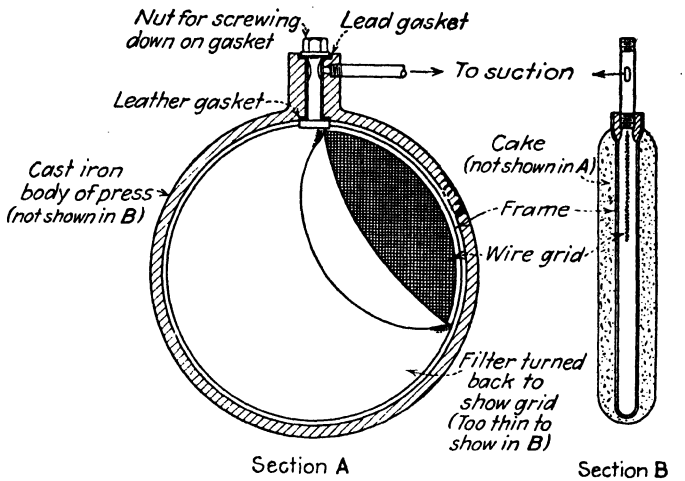


FIG. 174.—Filter leaf.

Pressure filtration is carried out by increasing the pressure on the liquid to be filtered by (1) gravitational means and (2) air or mechanical pressure on the liquid. Gravitational methods are used in simple filtration. However, syrupy or viscous liquids such as oils or copaiba may be filtered by pouring the liquid into a long filter bag enclosed in a long metal tube. This column of liquid produces sufficient pressure by gravity so that the liquid filters rapidly at the bottom of the tube.

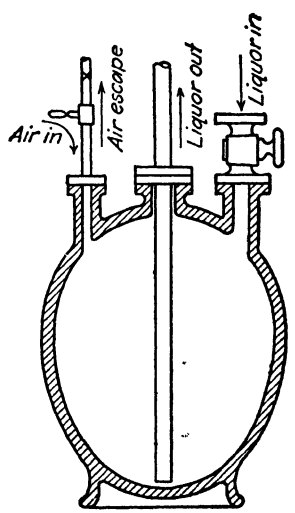


FIG. 175.—Montejus filter.

Mechanical or air pressure on the liquid is successfully employed in the Montejus filter (Fig. 175) and the filter press (Figs. 176, 177, 178).[1] Since liquids to be filtered are practically noncompressible, any pressure applied will force the liquid through the filtering medium. These pieces of apparatus are generally used

[1] JOHN W. COOPER. "Tutorial Pharmacy," Sir Isaac Pitman & Sons, Ltd., London, 1941, pp. 275–281.

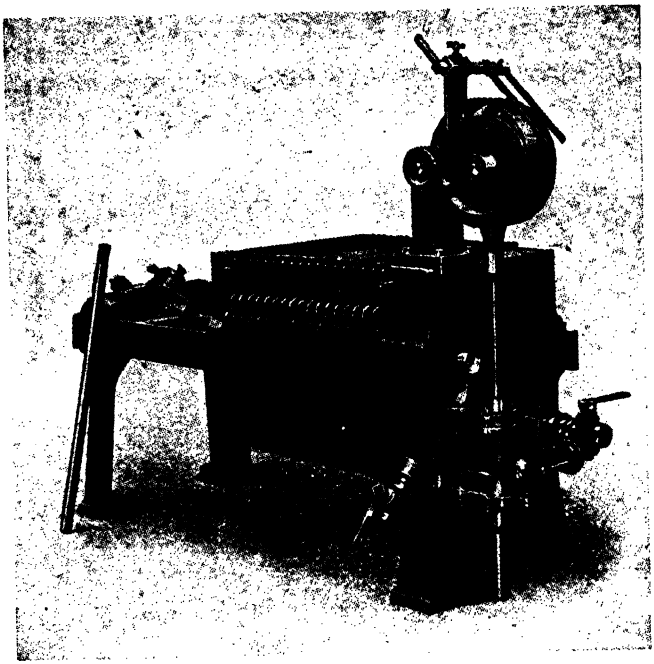


FIG. 176.—Filter press.

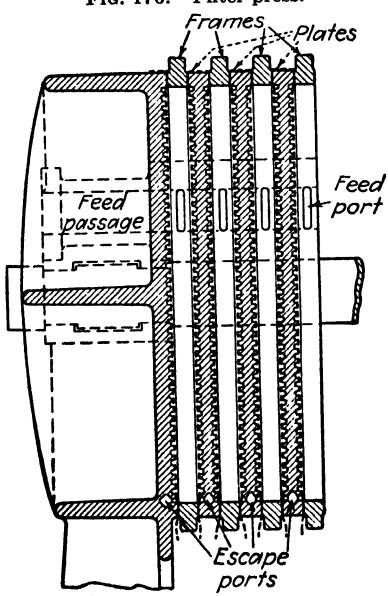


FIG. 177.—Section of flash-plate type of filter press.

in large-scale filtrations and will not be described here, their description and utilization being more properly included in a course in manufacturing pharmacy.

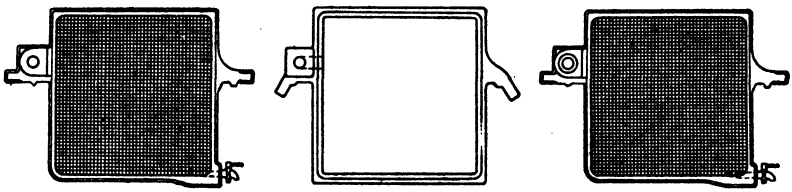


FIG. 178.—Plates and frame of a filter press.

Semimicro- and **microfiltration,** or **ultrafiltration,** assemblies are often necessary when minute quantities of material are to be filtered. This may be the case in inorganic and organic qualitative and quantitative analysis when it becomes necessary to recover small amounts of insoluble substances from liquids and to weigh or purify them. Among the many assemblies recommended for this purpose, two will be described because of their simplicity and ease of construction (Fig. 179).[1] The lower conical half of the glass cup of an Ostwald pycnometer is used with a filter disk, forming a fine filtering device similar to a Büchner funnel. The vacuum chamber is made by cutting off the bottom part of a large, strong-walled test tube provided with a side arm, and all joints are sealed tightly. This apparatus is serviceable in crystallizing and purifying small quantities of materials. A platinum disk may be made by perforating a small piece of foil with a needle and forming it into a disk of the same size as the tip of the filtering head. Koone's apparatus may be

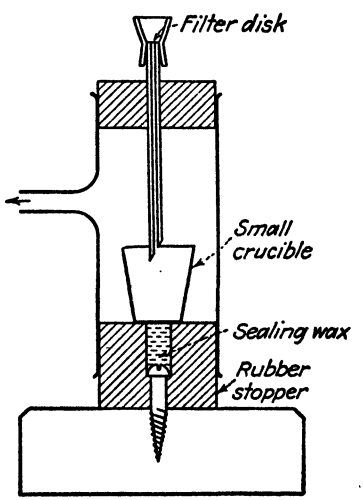


FIG. 179.—Apparatus for ultrafiltration.

[1] H. YAGODA. *Chemist-Analyst* **24** (No. 3), 20 (1935).

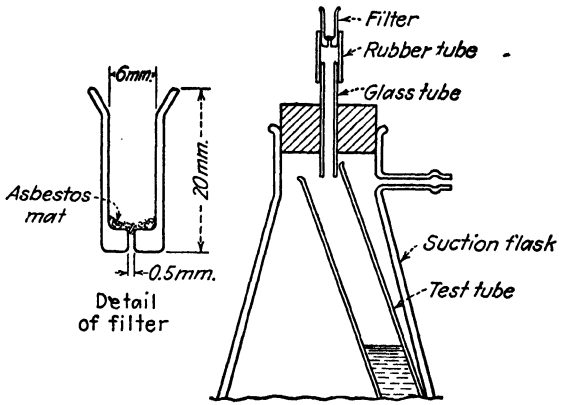


FIG. 180.—Microfiltration assembly.

easily constructed of materials available in the laboratory.[1] The filter crucible is small (1 to 1.5 Gm.), and the precipitate is kept compact, which permits the use of a minimum amount of wash liquid and facilitates the resolution of the precipitate if this step is necessary (Fig. 180).

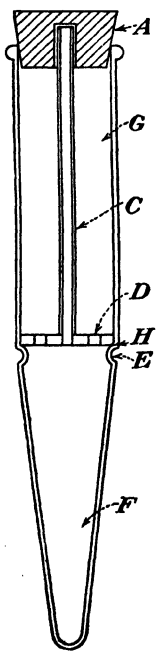


FIG. 181.—Centrifugal tube filter.

Separation of solid substances from a liquid when relatively small amounts of material are being used often presents considerable difficulty, especially when the specific gravity of the solid is close to that of the liquid. Perrine and Kump[2] have designed a filter that overcomes this difficulty (Fig. 181).

This tube is easy to construct from inexpensive material; it conforms in dimensions to the ordinary centrifuge tube and will fit into apparatus designed to take such tubes; the only substances that can come into contact with the contents of the tube are glass and filter paper; the filter may be used at high or low temperatures. A constriction *E* is made in a pyrex centrifuge tube (15 cc.) in such a position that the lower part of the tube *F* will be only slightly smaller in capacity than the upper part *G*. The filter plate

[1] ERNESTINE KOONE. *Chemist-Analyst* **27** (No. 1), 18–19 (1938).

[2] THEODORE PERRINE and WILLIAM KUMP. *Ind. Eng Chem. Anal. Ed.* **11**, 658 (1939).

D, through which holes have been ground, is made to rest on the shoulder *H*. The filter stem *C*, a 3-mm. pyrex tube, permits equalization of pressure between the chambers *F* and *G*. A filter paper is cut to fit inside the centrifuge tube, with a small central hole to take the filter plate stem. One or more papers may be fitted with the help of a glass rod. The mixture to be filtered is poured onto the filter and centrifuged after insertion of the rubber stopper *A*. The filtrate can be drawn off through the filter stem by means of a capillary dropper. The residue on the filter can be removed almost quantitatively by withdrawing the filter plate. In order to use the filter at temperatures above or below that of the room, the substance undergoing treatment, the filter, and the tube shield are preheated or precooled, and the substance is then rapidly transferred to the filter and centrifuged.

Metafiltration is filtration through apertures of a prearranged size in aseptically devised metallic or other structures; the

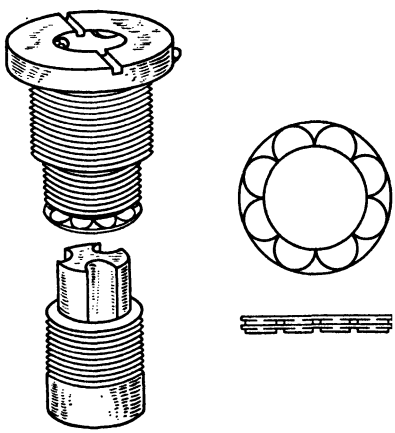


FIG. 182.—Metafilter ring (right) with surface view of scalloped ring and vertical section of two rings in position.

passage of particles above a corresponding diameter is thus prevented, while, by the simultaneous use of a filter bed, the fineness of filtration can be brought to the point usually considered accessible only to ultrafilters (Fig. 182).[1] This type of filtration includes filters with renewable filter beds and filters with renewable pockets; for filter beds, powdered or activated charcoal, infusorial earth, magnesium carbonate, and silica are used.

Streamline filtration is accomplished by means of a column of paper disks compressed together and pierced through the center

[1] *Chemist and Druggist* **132** (No. 3129), 65–70 (1940).

to form a conduit for the filtered liquid. The liquid to be filtered is forced by pressure or drawn by vacuum through the paper column to the inner conduit; the inequalities of surface

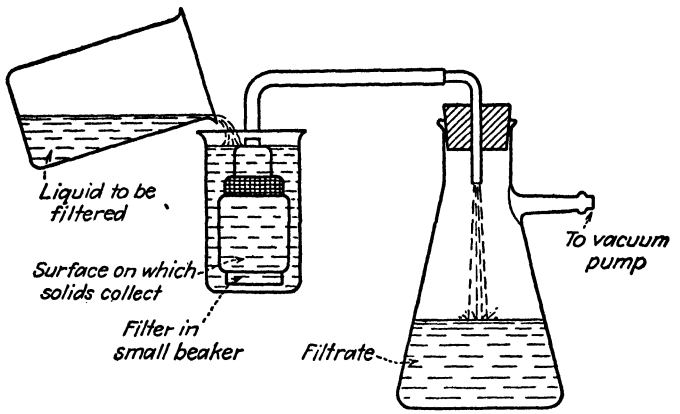


FIG. 183.—A laboratory streamline filtration assembly.

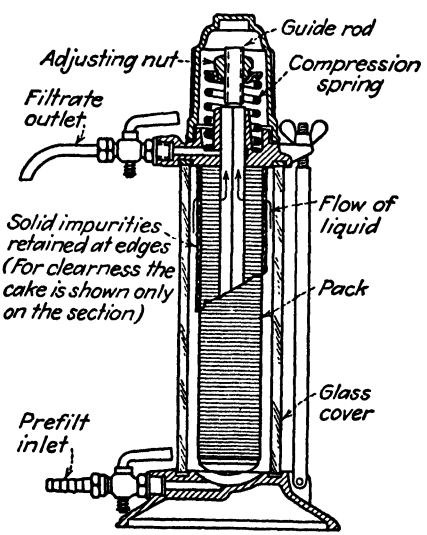


FIG. 184.—Streamline filter.

between the separate sheets form passages of an almost molecular fineness (Figs. 183–184). Each pack is mounted on a square rod; this leaves a space in the cylindrical bore of the paper column

through which the filtered liquid passes, and the solid particles are filtered from a cake on the outer surface of the column. Gradually the accumulating matter reduces the rate of filtration, but a reversed flow of compressed air removes the whole of the cake and restores the filter to its original condition. The streamline filter is especially suitable for analytical purposes, for acids and strongly alkaline liquids, and for lubricating, insulating, fuel, and edible oils and aqueous liquids.

Acid-resisting filtering materials include infusorial earth and porcelain filter tubes as well as porous ceramic filter tubes and

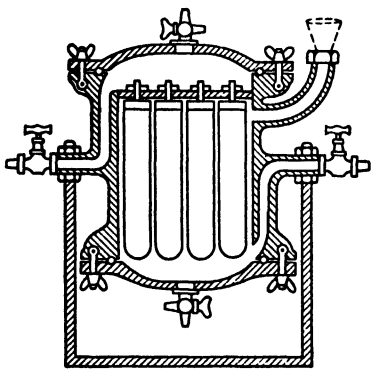


FIG. 185.—Multiple-candle Berkefeld filter.

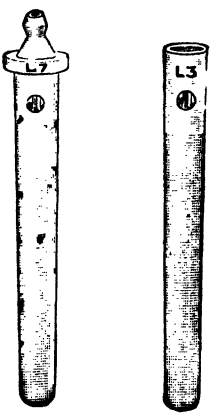


FIG. 186.—Filter candles.

disks. Their advantages are (1) regulated porosity and permeability, (2) higher resistance to aggressive chemicals, (3) good resistance to chemical shock and to high temperatures, (4) high mechanical strength and adaptibility for use in various types of filter, and (5) regularity of pore distribution. They are adaptable for use in suction, pressure, and rotary filters and centrifuges and are available in a variety of shapes and sizes suitable for gas and oil filtration. Screens of metal cloth for filter presses as well as various types of metal wire are marketed.[1]

Bacterial Filtration.—Bacterial filtration is discussed in greater detail under **Sterilization** (page 388); a complete treatment of the subject belongs properly in a course in **bacteriology.** It is a

[1] *Ibid.*

means of bringing about almost complete sterility of pharmaceutical products, such as ampul solutions (Injectiones U.S.P. XII), that might be injured by heat. The principal types are the (1) Berkefeld filter, (2) the Pasteur-Chamberland filter, (3) the Mandler filter, and (4) the Seitz filter (Figs. 185 to 188).[1] The first three are filter candles consisting of hollow cylinders of compressed infusorial earth or porcelain, provided with suitable endpieces with threaded nozzles for mounting.

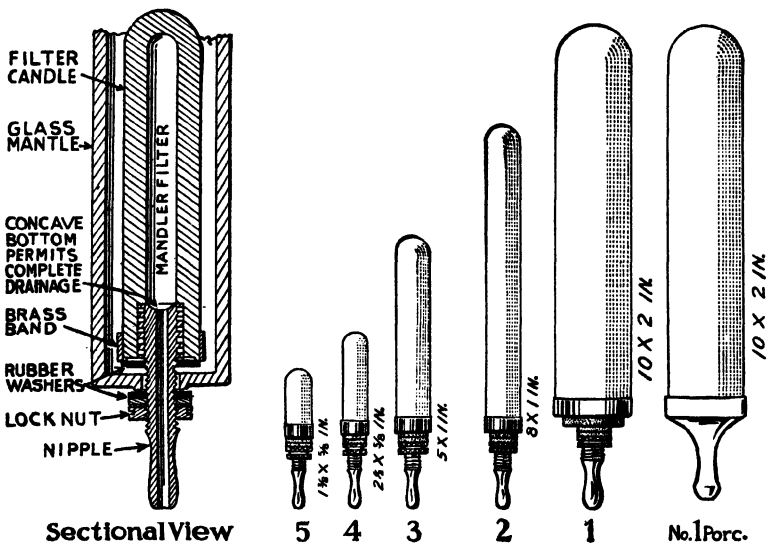


FIG. 187.—Sectional view of Mandler filter and candles.

The liquid to be sterilized is filtered by pressure or suction. The filters may be of the single or multiple types; they are sterilized before use, and the absence of leaks must be assured. Sizes vary from 20-cc. filters with 250-cc. filter flasks to filters of 2 to 3 L. with correspondingly larger filter flasks. The porcelain filter is finer but slower than the Berkefeld filter of infusorial earth and is reputed to remove filtrable viruses as well as bacteria. It is effective in the filtration of gargles, eyewashes, alkaloidal solutions, etc. The cleaning of candles is a difficult task, best accomplished by heating to redness in a muffle. The Seitz, or asbestos, bacterial filter consists of asbestos com-

[1] *Chemist and Druggist Ann. Machinery* No. 1 (1938), p. 93.

pressed into a disk, through which the liquid is forced. It is especially effective and rapid in working with large quantities of liquids.[1]

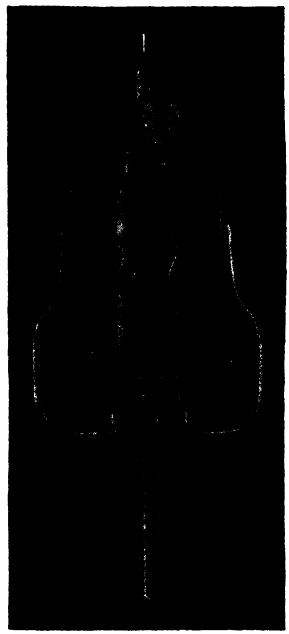


FIG. 188.—A Seitz pressure and vacuum filter.

Sintered-glass, or fritted-glass, filters may also be used for bacterial filtration. Berry,[2] by means of Beckholder's formula, reports the pore size for the Pasteur-Chamberland, Berkefeld, Mandler, Doulton, and sintered-glass filters. Sintered-glass filters are efficient when the **pore value** is not more than 2.5 μ; the Pasteur-Chamberland filter has a pore value of 1.3 μ and the Mandler of 2.6 μ, indicating that the former is practical for pharmaceutical sterilization. The task of cleaning this type of filter is a difficult one, but it may be accomplished by placing the filter in a dichromate–sulfuric acid cleaning solution for a period of time.

Centrifugal Filtration.—Centrifugal filtration is known also as centrifugal **separation, expression, straining,** and **decantation.** It is a valuable means of separating both solids and liquids from liquids by employing centrifugal force. The process is particularly valuable in washing and drying crystals, precipitates, and fabrics, in obtaining precipitates of blood, in urine analysis, and in the removal of bacteria from products, fats from milk, and fruit juices from pulp.

This form of separator may be provided with a removable bowl, which, with fittings supplied separately, can be assembled for use in any of the following capacities: (1) as a clarifier for the removal of suspended solids from a liquid; (2) as a separator for the continuous separation of two immiscible liquids, with simultaneous extraction of suspended solids; (3) as a clarifier

[1] F. WOKES. *Pharm. J.* **136** (1936); *Quart. J. Pharm. Pharmacol.* **9**, 460–1 (1936); *Pharm. Abstracts* **3**, 399 (1937).

[2] H. BERRY. *Pharm. J.* **139**, 267–8, 294 (1937). *Pharm. Abstracts* **3**, 485–6 (1937).

for small batches of liquid; (4) as a washing separator for the intimate mixing of two immiscible liquids, followed by their complete separation (as a solvent extraction).[1]

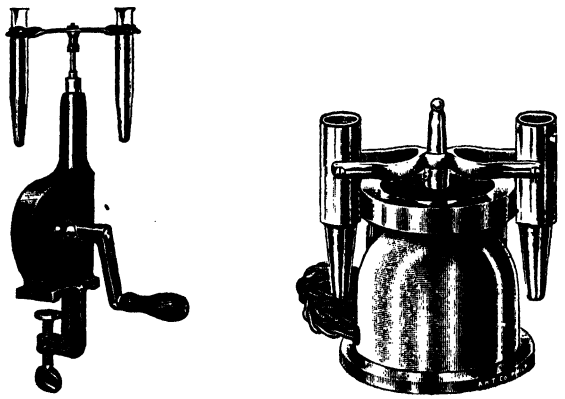


FIG. 189.—Small centrifugal machines.

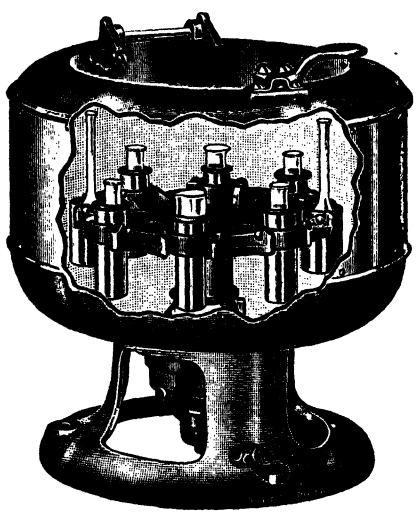


FIG. 190.—Large centrifugal machine.

The efficiency of the process depends on the velocity, although according to Shapiro,[2] in designating results involving the use of a centrifugal machine, the force compared with gravity (*i.e.*,

[1] *Chemist and Druggist* **132** (No. 3129), 65–70 (1940).

[2] H. SHAPIRO. *Ind. Eng. Chem. Anal. Ed.* **7**, 25 (1935).

relative centrifugal force) should be specified rather than the number of revolutions (*i.e.*, speed or velocity). The centrifugal force C in dynes is equal to $4\pi^2n^2R$ where n is the number of revolutions per second and R is the radius in centimeters. Relative centrifugal force equals $C/980$ compared with gravity.

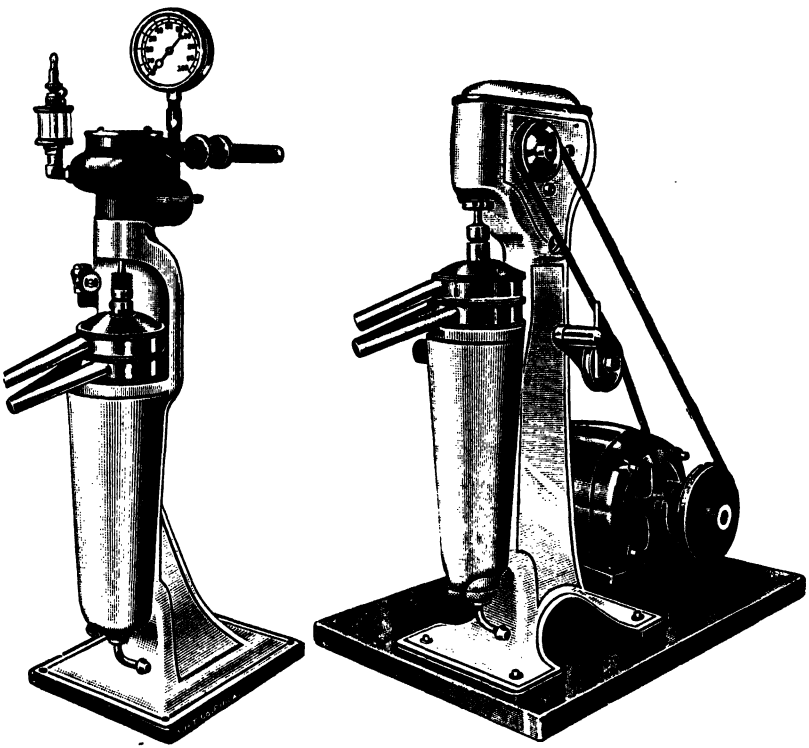


FIG. 191.—High-speed centrifugal machines.

The centrifugal machine may be hand or power driven and may be of two distinct types involving (1) the separation of the solid by centrifugal force and decanting the clear liquid, as the heavier particles are affected more strongly by this force; and (2) the separation of the liquid through flotation or through a porous or perforated vessel.

Several machines for small-scale use have been designed at reasonable prices (Fig. 189). Other recommended and more expensive large-scale machines are also shown (Figs. 190 to 192).

Rules for Conducting Filtration.—We have dealt extensively, although not exhaustively, with filtrations of the more important types. Certain simple rules should be observed at all times. These may be outlined as follows:

1. The speed of filtration, in using the plaited or pharmacist's filter, may be greatly accelerated and the filter made more durable by twisting the apex of the filter and inserting the latter firmly into the upper end of the funnel stem. This lends support

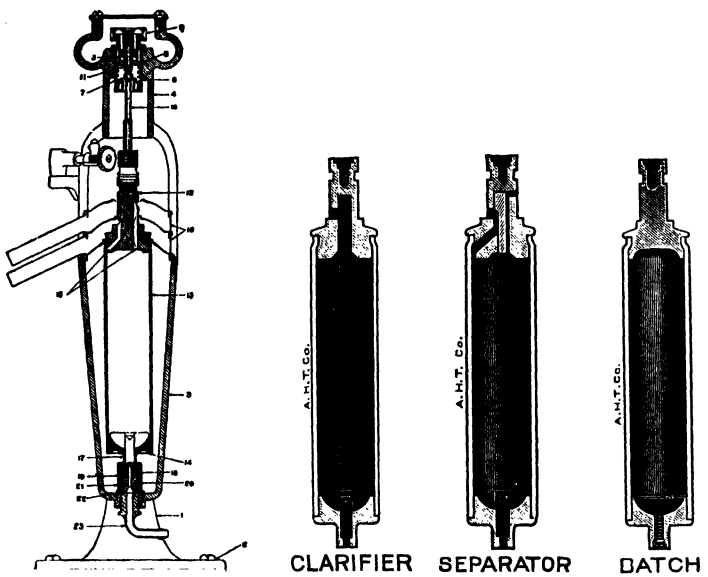


FIG. 192.—High-speed separators and parts to conduct various types of separation.

to the bottom of the filter paper when a large funnel and filter paper are used in filtering large quantities of material.

2. In simple filtration it is advisable to wet the filter paper so that it may be made to adhere to the funnel as firmly as possible when the liquid is added; this also aids in washing off shreds and linters from the paper, especially when an inferior grade of paper is used. It is advisable to wet the paper with the liquid that serves as the solvent or continuous phase. For example, if an aqueous preparation is being filtered, wet the filter with water; if an alcoholic or hydroalcoholic preparation,

wet the paper with alcohol or diluted alcohol of the approximate strength; if a chloroformic preparation, wet the paper with **chloroform** and **not water.** Fats and oils are usually filtered through a dry filter, and in such cases hot filtration will save time.

3. If the liquid to be filtered is highly alkaline or acid or contains a very fine precipitate or is very dense or hot, a double filter or an asbestos filter is indicated.

4. If large amounts are to be filtered, the paper should be supported at its apex by a filter cone of parchment paper without a tip or by a loose pad of cotton or glass wool, a strong gauze; or a small porcelain sieve or a double filter should be used. A filter may also be strengthened by placing at the apex a platinum cone or some other support.

5. Volatile liquids should be filtered in a filter provided with a cover and with the funnel inserted into the receiving flask through a cotton plug placed in the neck of the flask.

6. In pouring liquids into a filter the liquid should always be poured on the side of the filter, never into the apex, and a guiding rod should be used to direct the stream onto the filter.

7. A filter that is **too large** for the funnel should never be used, for this makes an unsightly apparatus, indicates carelessness in technique, and causes loss of liquid by increased evaporation of the liquid from the paper exposed above the funnel.

8. A funnel should be selected of sufficient size to accommodate effectively the amount of liquid or solid present. **Do not use a small filter in a large funnel.** The edge of the filter paper, when placed properly in the funnel, should be 0.5 to 1.0 cm. from the top of the funnel. This prevents loss by evaporation, "creeping," or running over. If the filtrate is desired, a plaited filter may be used; if the residue (precipitate or sediment) is wanted, use a smooth filter so that the solid may be easily removed (Fig. 193).

9. The funnel support should be adjusted so that the tip of the funnel stem will touch the side of the receiving vessel; thus loss by splashing and excessive evaporation is prevented.

10. The bottle should never be used as a funnel support. In filtering into a receiver with a small mouth such as the customary prescription bottle, there should be sufficient space between

the funnel stem and the neck of the bottle to allow for the escape of air as the filtrate flows into the bottle.

11. In resorting to continuous filtration, it is advisable to effect a preliminary separation of the larger particles by straining.

12. At the prescription desk it is often necessary to filter small amounts of dye solutions. These always present a problem when it comes to cleaning the apparatus. The staining may be avoided by rolling a piece of parchment paper into a cone of such dimensions as to hold the filter paper and yet permit insertion into the neck of the container as a support. After the filtration is completed, the papers may be discarded.

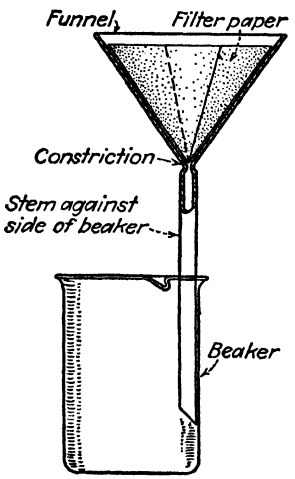


FIG. 193.—Proper assembly for simple filtration.

13. In using the asbestos mat with a Gooch, or other, crucible and a Büchner funnel, the holes have a tendency to become clogged or filled under the influence of strong suction and thus slow up the filtration or even stop it entirely. This tendency may be obviated completely and the speed of filtration increased many times by interposing a thin layer of glass wool ahead of the asbestos pad by merely laying or tamping it on the bottom, the asbestos suspension being then poured through in the usual manner.[1]

COLATION

Colation (Latin *colare*, to filter, to strain) is the process of separating large solid particles from liquids by pouring the mixture on a cloth or other porous medium (colatorium) that permits the passage of the liquid and retains the solid. It may be considered a type of filtration or a preliminary step to filtration. Generally the liquid is the portion desired; this is called the colature. The process is one that is much employed by the layman, especially the housewife, as well as the pharmacist, since it is fairly rapid and involves no great outlay for apparatus.

[1] G. W. PAWEL. "Facilitating Filtration," *Chemist-Analyst* **29**, (No. 4), 93 (1940).

The essential apparatus is a **straining medium** and a **strainer support,** or **frame.** The straining media, or strainers, are most generally of cloth, such as Canton flannel, muslin, woolen material, and cheesecloth, supported in a square form of wood provided with projections to hold it during straining. This frame is called a **tenaculum** (Fig. 194). Other forms of strainer may be screens of iron, enamelware, and porcelain, as well as sieves, which are provided with cotton, oakum, or wood wool. After the excess liquid has been strained from the insoluble matter, more liquid may be removed by expressing.

For small-scale straining at the prescription desk, the convenient combination hard-rubber strainer and powder funnel (see Fig. 152) may be used; or the wet straining cloth may be tied on the edge of a wide-mouthed container and the liquid poured onto it, the residue being expressed after the liquid has drained off (see Fig. 130). Great pressure should be avoided; it is preferable to rinse the residue with a liquid (water, alcohol, etc.).

FIG. 194.—Strainer and frame.

In simple straining, the colature is seldom clear. However, there are strainers that are efficient enough to produce clear colatures. These may be made of a fairly thick felt of wool or hair. They are used for melted fats, petrolatum, waxes, oils, syrups, and elixirs. Such strainers have been called "leg-of-mutton" strainers or "Hippocrates' sleeve" because of their shape. They are supported in a frame by means of rings or a hoop and are suspended within a container to avoid evaporation due to air currents (Fig. 195). They are expensive and difficult to clean, and often the odor of the materials strained through them is retained for long periods of time, even after subsequent washings.

Other convenient forms of strainer are of metal and are called **colanders** or sieves; they may have a strainer cloth for more complete removal of the solid matter. Presses may be used, also; or a ring may be attached to a funnel to which the cloth is held by means of hooks.

If a cloth is used as a strainer, it should be colorless (not dyed) and should be washed before being used to remove sizing materials

such as gelatin, albumin, glue, starch, or mineral filler. This is accomplished by soaking in cold water and then boiling in distilled water.

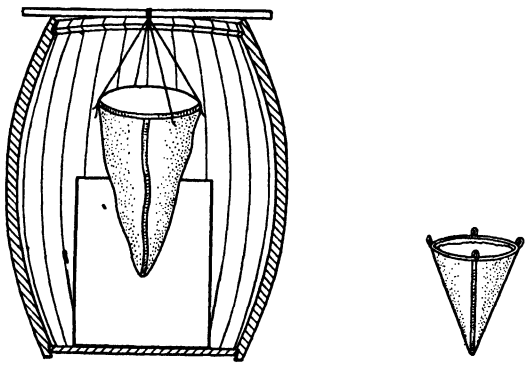


FIG. 195.—"Leg-of-mutton" strainers.

DRYING BY ABSORPTION

Another means of separating a solid from a liquid (particularly small quantities of the latter) in order to obtain the solid in a dry condition is **drying by absorption** (see page 519). In the laboratory, solids, which often cannot be dried by the usual methods employing heat, may be dried in small quantities between filter papers, on porous porcelain plates, or by the slower desiccator method. Larger quantities may be dried quickly by resorting to vacuum and centrifugal filtration.

A pharmaceutical process based upon this form of drying that is not much used at the present time is **trochiscation.** This is a method of obtaining a solid by shaping a wet pasty mass, or magma, often obtained by **elutriation** (page 525) into the form of a dry mass, generally cone-shaped. The wet mass is placed in a conelike funnel of heavy paper—preferably parchment—or in a funnel held on a support; upon tapping, the material is exuded and allowed to fall upon porous material, which will dry out the substance to form a conical mass. Prepared or Drop Chalk U.S.P. XII is manufactured by this process.

DECOLORATION, OR DECOLORIZATION

Decoloration, or decolorization, is a process whereby liquids or solutions are deprived of undesirable colors by filtration

through suitable media or by chemical means. The media used are finely divided substances that have the property of mechanical absorption (page 488) and/or selective adsorption (page 489) for the substances causing the color.

For most laboratory purposes, the charcoals are most commonly used—bone, blood, and wood charcoals (Carbo Activatus U.S.P. XII, Norite, decolorizing charcoal or carbon). Other substances for this purpose are the clays, such as bentonite, kaolin, fuller's earth, and infusorial earth. Care should be taken in the selection of the decolorizing agent in treating solutions that contain other substances besides coloring matters, for the composition of the solution proper might be changed owing to the removal of such important constituents as organic acids, glucosides, alkaloids, and bitter and neutral principles.

This process is of great importance in sugar refining, in making syrups, in purifying fats, oils, petrolatums, etc., and in the pharmaceutical laboratories in preparing superior products devoid of foreign coloring matter and in purifying solutions prior to analysis.

The process is usually accomplished by digesting, or shaking, the liquid mixture with the decolorizing agent and then filtering, or allowing the liquid to percolate slowly, through a column of the medium. The liquid should be returned or more of the agent used if the former has not lost its color. After a time the agent will no longer decolorize. It may then be discarded or rejuvenated, as in the case of animal charcoal, by heating.

Clarification

Clarification (Latin *clarus*, clear, + *facere*, to make) is a process of removing from liquids substances that interfere with the transparency of the finished product. It may or may not be followed by filtration. It also has to do with the separation of finely divided, suspended substances from liquids as a solid, compact residue, in order to carry on with greater facility the processes of decantation, straining, and filtration. It is also accomplished by mechanical withdrawal on the surface, as in skimming, or in chemical processes by the formation of precipitates.

Turbidity is often encountered in pharmacy in the preparation of elixirs, spirits, and other products containing oils to which water has been added in the course of their preparation. In general, clarification involves, as already stated, the uniting of small particles into larger ones (agglomeration) by allowing the liquid or solution to stand for a time, a deposit or sediment being thus obtained (sedimentation), or by heating certain albuminous materials to bring about coagulation, as in fruit juices. Purified or clarified honey was formerly prepared by heating; the wax would rise to the top, carrying with it other matter, and then be skimmed off. Heat also changes the viscosity of the liquid mixture, allowing the heavier particles to settle out or the lighter ones to rise to the surface to form a scum, which may then be removed by skimming. The process of **digestion** often directed in chemical procedures brings about an enlargement of solid particles by heating and standing.

Chemical clarifying agents include **tannic acid** for the separation of gelatinous and pectinic substances and **gelatin** for the precipitation of tannins as in wine making. Unusually small amounts of these agents are necessary, and there should not be an excess of either of the two substances. Tests for their absence should be made after completion of the process. Tannic acid may be detected by the use of ferric chloride test solution and gelatin by tannic acid test solution.

Agents acting by mechanical surface withdrawal are paper pulp (syrups), talcum (tinctures, syrups, elixirs, extracts), alumina (honey), egg albumin, burnt alum (spirits—20 Gm. per L.), infusorial earth, etc.

The choice of agent depends on the type of liquid being clarified; it should be one that will give as complete clarification as possible with one treatment. When egg albumin is used, it is always necessary to warm it to bring about coagulation and subsequent clarification by occlusion. The effectiveness of egg albumin may be increased by the addition of cellulose such as finely divided filter paper; this addition also facilitates filtration after clarification. Clarifying agents that must be boiled are usually removed by skimming. Some clarifications may also be helped by adding substances of high specific gravity (talc, clay, etc.). These cause sedimentation of the impurities as a thick froth.

If talc is used, an excess should be avoided since it will float about in the liquid and run through the filter paper. The amount to be used may be determined by preliminary experiment.

Peyer[1] recommends the following clarifying powders:

Peyer		Dieterich	
Dried egg albumin	20	Dried egg albumin	40
Lactose	20	Lactose	30
Potato starch	10	Starch	20
Mix		Finely powder and mix	

For 1 L. use 1 to 5 Gm., shake frequently, let stand for several days at room temperature, and filter.

Filter aids (page 488) such as talc, infusorial earth, kaolin, bentonite, fuller's earth, magnesium oxide, magnesium carbonate, and calcium phosphate bring about agglomeration by absorption and enlargement and will remove finely divided particles of oils, etc., suspended in liquids. Care should be taken that undesirable reactions are not given to the clarified product by a solution of a small portion of the clarifying agent. Paper and wood pulp, by enlargement and obstruction, help to clarify, as does the presence of alumina and sand in water purification and clarification. Egg albumin coagulated by heat tends to surround and entangle particles, which may be removed by subsequent filtration. It may also be added to liquids containing tannins, with which it is incompatible; the resulting precipitate aids in clarification.

The adjustment of liquids to a definite hydrogen-ion concentration may aid in clarification, as will fermentation, since many substances such as pectins and albumins are soluble in natural juices but insoluble in alcoholic solutions; milk added to products acid in reaction will precipitate the casein, which settles out, carrying with it solid particles. **Coagulation** and **flocculation** in colloidal chemistry are processes closely related to clarification.[2]

THE SEPARATION OF LIQUIDS FROM LIQUIDS

Such a separation, in general, involves two or more immiscible liquids; *i.e.*, layers are formed that may be separated by the

[1] WILLY PEYER. "Hager's Pharmazeutische Technische Manuale," J. A. Barth, Leipzig, 1931, p. 412.

[2] JAMES F. COUCH. *Am. J. Pharm.* **94**, 92–7 (1922).

use of a siphon (page 477), by pipettes—graduated and ungraduated—using suction by pump or mouth, or by a syringe or medicine dropper. The centrifugal machine (page 507), special types of receivers such as Florentine receivers (page 353), and separatory funnels (Fig. 196), which may be of various shapes, with or without ground-glass stoppers, are other means of bringing about this type of separation.

Separations of liquids from liquids are carried out in the purification processes of alkaloidal assays, in the separation of

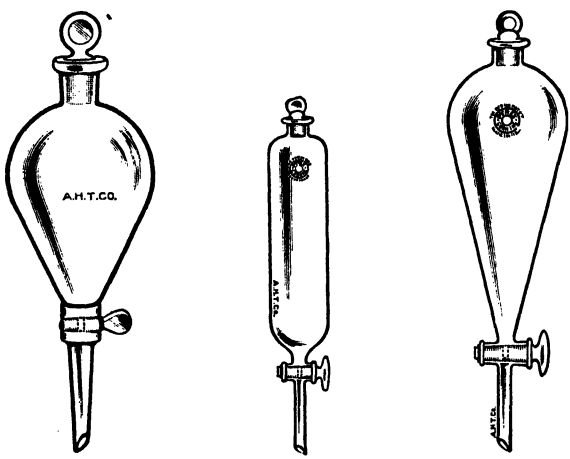


FIG. 196.—Separatory funnels.

volatile or other oils from water in steam distillation, etc., and in the case of accidental contaminations and admixtures.

Small quantities of water may be separated from other liquids by the use of effective drying agents such as anhydrous forms of calcium chloride, sodium sulfate, calcium sulfate, magnesium sulfate, phosphorus pentoxide, magnesite, and dehydrite.

SEPARATION OF GASES FROM LIQUIDS AND FROM GASES

This type of separation, while important commercially, is not of great concern to the pharmacist except in an incidental way. Certain substances such as the charcoals and clays have the property of adsorbing on their surfaces large amounts of gases, usually with a marked evolution of heat since the change involved is closely related to liquefaction.

Deodorization is a process of depriving substances of odors due to gases, liquids, or solids; these odors are generally obnoxious. It is accomplished by the use of adsorbents, *i.e.*, by passing the gaseous mixture through substances or solutions that have a particular affinity for the offensive gas or by the use of some substance that itself has an odor, and by **aeration.** The latter process is the removal of gases from a liquid by exposure to air and sunlight, as in the purification of drinking water that is allowed to flow in cascades, from spillways, fountains, and

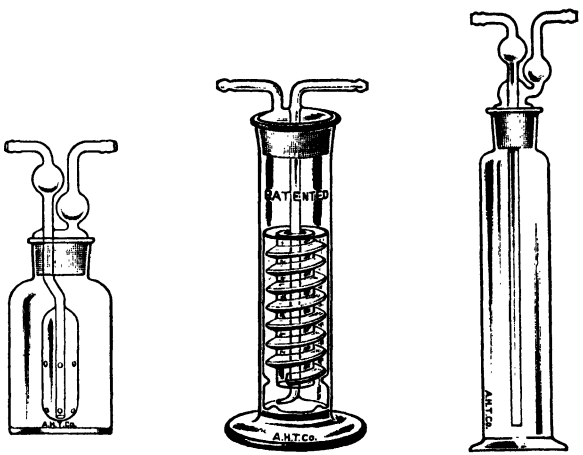


FIG. 197.—Absorption bottles.

spraying nozzles, the water being thus exposed in thin layers or small particles to air and sunlight.

The reverse of these processes, the removal of small amounts of liquids—particularly moisture from gases—is often necessary both in the laboratory and on a commercial scale. This is generally accomplished by the use of drying agents in appropriate absorption and washing bottles (Fig. 197). Bower[1] has determined the comparative efficiencies of various drying agents for gases. The order of efficiency at 30°C. for the materials studied (with the amount of residual water in milligrams per liter of air-dried gas) follows: copper sulfate, 2.8; calcium chloride (granular), 1.5; calcium chloride (technical anhydrous), 1.25;

[1] J. R. BOWER. *Bur. Standards J. Research* **12**, 241 (1934); *Yearbook Am. Pharm. Assoc.* **23**, 254 (1934).

zinc chloride (sticks), 0.98; barium perchlorate, 0.82; magnesium perchlorate, 0.031; silica gel, 0.030; potassium hydroxide (sticks), 0.014; aluminum chloride, 0.005; calcium sulfate (anhydrous), 0.005; calcium oxide, 0.003; magnesium chlorate, 0.002; barium oxide, 0.00065.

Occasionally it is necessary to separate a gas or gases from other gases as in the case of the analysis of flue gases and fuel gases and the removal of carbon dioxide from air. This is accomplished by the passage of measured quantities of the gaseous mixture through appropriate solutions or solids in gas-absorption bulbs, bottles, or vessels (Fig. 198).

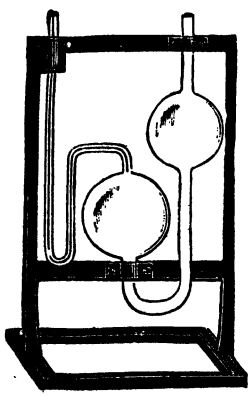


FIG. 198.—Hempel gas-absorption pipette.

SEPARATION OF SOLIDS FROM SOLIDS

This section deals with the separation of solids as such and does not refer to separations by which one solid may be separated from another by the use of appropriate solvents (see Chap. XII).

The simplest process of this nature is **garbling,** which is the separation of impurities, decayed matter, and adulterations from crude drugs after drying, from fresh herbs, etc. It is accomplished principally by hand.

Other means of separation—for laboratory and commercial operations—include blowing and fanning. Light particles are thus removed from heavier particles, as in the cleaning of seeds and grains in order to remove weed seeds, chaff, etc.

Sifting (sieving, or screening) is the most important means of separating solids from each other. It is primarily a process of separating coarse particles from finer ones, particularly powdered substances. It is accomplished chiefly by the use of **sieves,** or **screens,** and **bolting cloth.** Its objects are, at least, twofold, (1) to grade chemicals and solid preparations and drugs that are uniform in composition into various degrees of comminution (fineness) and (2) to mix powders that do not readily mix by other methods or to distribute a small amount of an active or potent substance throughout a large quantity of a diluent.

Sieves may be of various shapes—round, oval, square, rectangular, or in the form of a scoop. High-grade sieves are numbered according to the number of wires per linear inch. For example, a No. 10 sieve has 10 parallel wires per linear inch, with openings for the particles to pass through of less than 0.01, or $\frac{1}{100}$, sq. in.; a No. 20 sieve has 20 wires per linear inch and openings of less

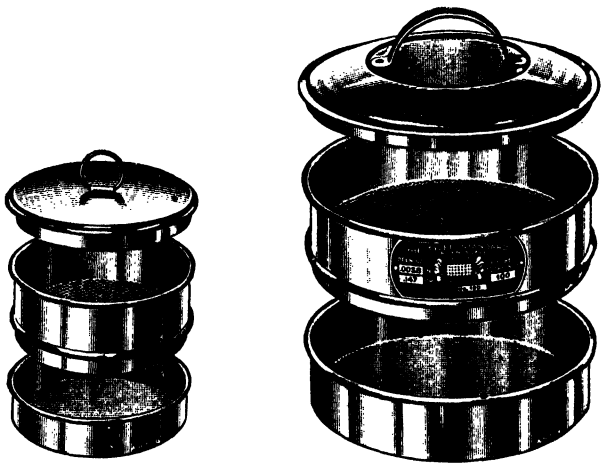


FIG. 199.—Sieves.

than 0.0025, or $\frac{1}{400}$, sq. in. and is therefore four times as fine as the No. 10 sieve. Sieves are made of brass or bronzed wire, iron or tinned iron wire, hair, cane, or cloth (Fig. 199). Those above a No. 120 mesh are usually made of bolting silk, which is a high-grade silk made of strongly twisted threads so that an even mesh is secured, with no tendency for surface fiber to flake off when in contact with preparations (Fig. 200).

TABLE XXVI.—SPECIFICATIONS FOR SIEVES

No. of sieve	Size of opening, mm.	Diameter of wire, mm.	Tolerance, average opening, %
10	2.000	0.760	±3
20	0.840	0.420	±5
40	0.420	0.250	±5
60	0.250	0.162	±6
80	0.177	0.119	±6
100	0.149	0.102	±6

The Bureau of Standards has established standard specifications for sieves, which, however, differ from those prevalent in Europe and elsewhere.

On the bases of these specifications the Pharmacopoeia (pages 583 to 585) has established standards for the uniformity of fineness for **vegetable or animal drugs.**

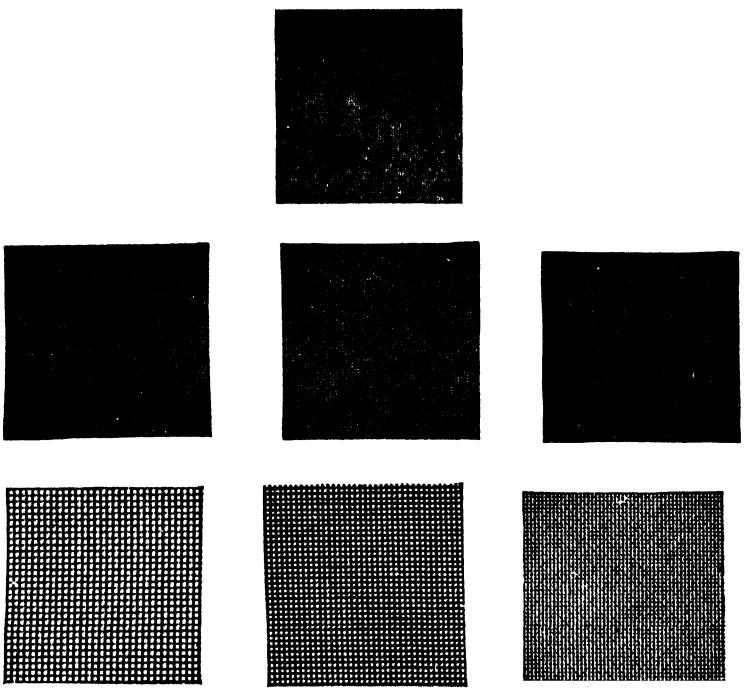


FIG. 200.—Various meshes of sieves.

A **very coarse powder** (No. 8) is one of which all the particles will pass through a No. 8 standard-mesh sieve and not more than 20 per cent through a No. 60 standard-mesh sieve.

A **coarse powder** (No. 20) is one of which all the particles will pass through a No. 20 standard-mesh sieve and not more than 40 per cent through a No. 60 sieve. In the case of **chemicals,** not more than 60 per cent will pass through a No. 40 sieve.

A **moderately coarse powder** (No. 40) is one of which all the particles will pass through a No. 40 standard-mesh sieve and not more than 40 per cent through a No. 80 sieve. In the case

of **chemicals,** not more than 60 per cent will pass through a No. 60 sieve.

A **fine powder** (No. 60) is one of which all the particles will pass through a No. 60 standard-mesh sieve and not more than 40 per cent through a No. 100 sieve. In the case of **chemicals,** a fine powder (No. 80) is one of which all the particles will pass through a No. 80 sieve.

A **very fine powder** (No. 80) is one of which all the particles will pass through a No. 80 sieve. In the case of **chemicals,** all the particles will pass through a No. 120 sieve.

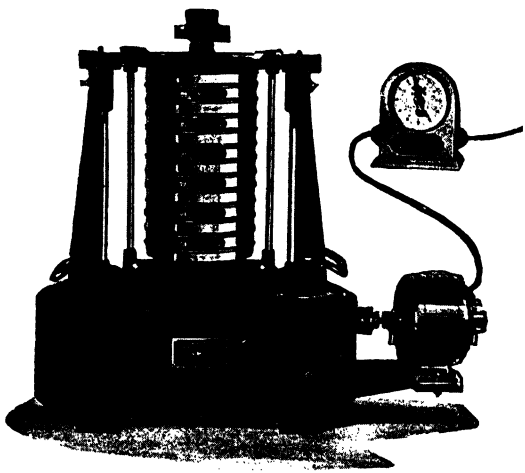


FIG. 201.—Sieve shaking apparatus.

A detailed procedure is also outlined (page 585) for determining the uniformity of fineness.

In simple **bolting,** the mixture is placed in a bag of smooth, thick uniformly woven linen or silk. After tying the bag, it is shaken continuously in a well-closed metal vessel, and by beating the bag on the walls of the vessel the finest particles are made to pass through.

For quantity production, the sifting of powders is accomplished by machines of various styles and designs. These are usually combination mixer-sifters and may be operated by hand or by power machinery. The sieves are usually in the form of cylinders that rotate about their axes, or they may be rectangular or circular screens that vibrate (Fig. 201).

Certain rules should be observed to carry out the process of sifting efficiently and to keep the sieves, which are relatively expensive, in good condition:

1. The material subjected to sifting should not be added in great quantity at one time, for this does not permit proper movement of the particles over the openings or their passage through them. This is especially true of the finer powders. Powdered materials may be transferred by use of a spatula or directly from a bottle or a sheet of paper.

2. After adding material to the sieve provided with a bottom, close tightly to avoid loss during the process.

3. Shake the sieve with a circular horizontal movement; then alternate with a vertical motion, accompanied by a vigorous tapping on the palm of the hand or on a hard surface, with as little disturbance as possible. If the sieve is a coarse one, the solid particles may be brushed through with a brush. Care must be observed in brushing a fine sieve since the wire has a cutting or shearing action on the bristles of the brush.

4. Do not force the particles through the openings. This treatment permanently injures the sieve, since the force used pushes the wires apart irregularly and permits the passage of larger particles than indicated by the sieve size.

5. A sieve should be carefully cleaned after each operation. This may be accomplished with a special soft sieve brush, by blowing air through the openings, or by washing with water or some other suitable solvent, followed by drying in air or in a drying oven at moderate heat. The sieve should then be stored in a dust-free place.

6. Very fine and fluffy substances such as magnesium oxide and magnesium carbonate can be bolted more effectively than they can be sieved.

7. In sifting, it is essential that all the solid particles shall be passed through the sieve unless otherwise directed. This is imperative in the case of vegetable drugs. Upon grinding such a drug the sizes of particles vary depending on the nature of the texture of the plant tissue. Also, medicinal principles, as a rule, are not distributed uniformly throughout the plant parts. For example, the glucosides of digitalis occur primarily in the veins (hard tissue), whereas the alkaloids of ipecac are

found in the soft tissue of the roots. Thus, in powdering and subsequent sifting of digitalis, the powder obtained will be deficient in glucosides unless all the portions that at first fail to pass through the sieve are further triturated and finally sifted through. In the case of ipecac root, the powder procured will be high in alkaloids, since the harder portions of the root, which are deficient in these substances, remain on the sieve; in order to attain a powder of proper pharmacopoeial alkaloidal strength, all the drug should be powdered and sifted. A powdered drug should never be separated into fine and coarse portions.

8. Sifting may be hastened by first passing the powder through a sieve of large mesh if the powdered substance consists of a single substance.

9. In using sieves for mixtures, the powders should be passed through the sieve two or three times. The resulting mixture should flatten out smoothly and be free from grains or streaks. All the powder should be thoroughly mixed again after sifting.

10. For sifting highly perfumed and flavored powders (tooth pastes, face powders, sachets), capsicum, cantharides, etc., individual sieves should be used. It is exceedingly difficult to remove all traces of odors in cleaning, and these might be transferred if the same sieves are used for other powders.

In a sieving analysis, a number of variable factors influence the process. These have been shown to be the personal factors, the nature of the powder, the weight of the powder, variations in sieve aperture, and, particularly, the time elements.[1,2]

Sifting operations are especially important in dispensing solids in powdered and divided forms, in the manufacture of toilet and cosmetic preparations, and in the production of flavors, various food products, soap powders, cleaners, starches, bluings, snuffs, dips, metal polishes, disinfectants, and insecticides.

Elutriation (Latin *elutriatus*, past participle of *elutriare*, to wash out) is the separation of coarse particles from fine ones; it depends on a difference in the mass of the coarse and fine particles. Those with the larger mass will settle more quickly than those with the smaller mass. As they approach varying degrees of colloidal state, the particles will tend to stay in suspension.

[1] C. K. WENTWORTH. *Am. J. Sci.* **13**, 399–408 (1927).

[2] H. HEYWOOD. *J. Inst. Fuel* **3**, 428–32 (1930); *Chem. Abstracts* **25**, 1714 (1931).

The rate of settling follows Stokes' law, $v = 2gr^2/9q$, where g is the gravitational constant, q is the viscosity of the liquid, v is the velocity of settling, and r is the radius of one of the particles. v may be ascertained by the formula $v = d/t$, where d is the distance through which a particle falls during time t, the centimeter and the second being used, respectively, as units of distance and time; and where r is known, the volume v may be calculated.

The process is generally applied to inorganic substances heavier than and insoluble in water and is used chiefly to separate particles in a paste prepared by **levigation** (Latin *levigatio*, a smoothing). The paste is mixed with a large amount of water and the mixture allowed to stand. Fine particles are separated from the larger and heavier particles that have already settled out; the fine particles in the upper layer are then allowed to settle. In the laboratory, any suitable vessel may be used; for industrial operations, **elutriation tanks** are employed. Substances prepared by this process are Prepared Chalk U.S.P. XII, Calamine N.F. VII, Bismuth Subnitrate U.S.P. XII, and similar inorganic compounds.

Solids may also be separated from each other by putting the mixture in a dense liquid. The light particles will then float, and the others will sink.

STUDY QUESTIONS

1. A hydraulic press has two pistons with cross sections of 16 and 96 sq. in., respectively. The small piston is operated with a lever of the first class with arms of 60 and 12 in. What pressure can be developed if a force of 120 lb. is applied at the longer lever arm?

2. Explain the principle of the filter press.

3. Four liters of Magma Magnesiae U.S.P. XII containing 12 per cent sodium sulfate as an impurity is subjected to the following lotions and decantations: (*a*) 3 L. of the clear liquid is first siphoned off; (*b*) the volume is again brought to 4 L. with water, stirred, and allowed to settle, and 3 L. is again siphoned off; (*c*) and (*d*) step *b* is repeated two more times. Calculate the amount of impurity in percentage and weight remaining in the magma after each decantation.

4. If a precipitate is washed by decantation three times and each time one-tenth the wash liquid remains behind, how many more times efficient is this procedure than if five-tenths the wash liquid is allowed to remain behind?

5. A precipitate of ferrous carbonate is prepared by the reaction $FeSO_4 + K_2CO_3 = K_2SO_4 + FeCO_3$, and the potassium sulfate (10 per cent) is washed from the precipitate in a 5-gal. vessel by decanting 4 gal. of the wash liquid each time. What percentage of impurity remains after the first, second, third, and fourth washings?

6. Explain the principle of the siphon; of the filter pump.

7. Why is hot filtration employed?

8. State five rules for filtration, and give three ways by which the process is accelerated.

9. Name the apparatus necessary to carry on suction filtration.

10. List the methods that have been recommended to facilitate filtration.

11. Why are some solutions decolorized and others not when treated with a decolorizing agent?

12. Name the types of apparatus used to separate liquids from liquids.

13. What is meant by the mesh, or number, of a sieve, or screen?

14. How does a No. 10 sieve differ from a No. 60 in the area or size of the openings?

15. Explain why it is imperative that all of a powdered drug being graded to a definite size shall be passed completely through a sieve.

16. Explain how one should obtain 20 Gm. of a powdered drug in No. 80 powder according to the methods for determining the uniformity of powders, as given in the Pharmacopoeia XII.

17. What law is in effect in elutriation?

18. Define (*a*) elutriation, (*b*) decantation, (*c*) garbling, (*d*) levigation, and (*e*) colature.

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CHAPTER XIX

THE STORAGE AND PRESERVATION OF DRUGS

To the layman the problem of storing and preserving drugs is likely to appear à simple one. Storage is regarded as a matter merely of placing drugs in containers and stacking these out of the way on convenient shelves. Preservation resolves itself into a matter of substantial packaging, loss through spilling, leaking, or evaporation being the only difficulty that is recognized. Little or no thought is given to the fact that the methods used to store and to preserve drugs frequently have a great influence on their potency as therapeutic agents and that there are many ways for correctly solving the problems of storage and preservation.

A large percentage of the medicines on the market today require special care in their storage and preservation in order to maintain their original therapeutic value. The extent of this percentage is not known even by the manufacturer, for relatively little research or study has been devoted to this phase of pharmacy. Enough investigational work has recently been finished, however, to establish the fact that many of our pharmaceuticals are neither properly stored nor properly preserved. Recognition of this fact is rapidly widening interest in research in this field.

The purpose of this chapter is to demonstrate by illustration the need for care in the keeping of drugs and to describe in a broad way some of the methods available both to the manufacturer and to the retail pharmacist for satisfactorily achieving this objective.

It will aid our study if from the beginning some of the many factors that influence or affect the deterioration of drugs are known. Some are well known and understood; others are recognized, but their operation is as yet not clear. Sometimes deterioration takes place without the cause even being identified. The more common factors known to be important in lowering the original potency or value of drugs are moisture, light, tempera-

ture, air, age, chemicals in contact with the drug either as part of a formula or as impurities, **insects** or **small animal life,** and **fungus** or **other plant growths.** The **volatility** of the active ingredient of the drug is often important in deterioration.

Which of these or any other factors are important in the destruction of a given drug must be determined by research. This is usually conducted by placing the drug under the influence of a variety of controlled conditions involving the effect of one or more of the possible deterioration factors. The degree of deterioration, which is a direct measure of the significance of any of the factors as a destructive force, is determined by various analytical procedures. Guarding against these factors of deterioration may be a physical or a chemical problem, or both.

Moisture.—Moisture is a major cause of deterioration in medicines. This is particularly true in the storage and preservation of dry powders. Deliquescent substances such as zinc chloride must be protected from moisture, or they will lump up in moist masses or, in extreme cases, will become liquid. Deliquescent chemicals thoughtlessly packaged in paper containers by manufacturers and wholesalers for distribution to retail pharmacists sometimes arrive at their destination so spoiled by moisture absorbed through the container as to be useless.

Alteration of the physical appearance of a drug is not the only disagreeable consequence of moisture absorption. **Ephedrine** must be stored so that it will be free from contact with moisture; otherwise, its solutions in oil will be turbid instead of clear, as they should be. Moisture accelerates the decomposition of dry **digitalis preparations,** and so the Pharmacopoeia directs that digitalis should be preserved under all conditions of storage and transportation in waterproof and airtight containers. The same instructions are also given for the preservation of **ergot.** Cod Liver Oil U.S.P., because of its standardized vitamin content, must be stored with unusual care.

Light.—Light, particularly direct sunlight, destroys the activity of many drugs. An understanding of how radiant energy functions as a destructive agent requires some knowledge of the quantum theory, as presented in a course in physics. Susceptible drugs are decomposed by light. Sometimes this action

is rapid; but in the majority of cases it is slow and, at first, unnoticed. The alert pharmacist can check on the action of light on his chemicals by watching for color changes in those exposed to its influence. **Tannic acid** will darken perceptibly, and so will the **bismuth salts.** **Aminopyrine** and **quinine** compounds, which are pure white, will become brown. White **calomel** will turn grayish black. The change of color in calomel indicates the gradual formation of free mercury and mercuric chloride, both of which are toxic. Amber bottles seem to be the most satisfactory containers for use in preventing such changes as light brings about. Some manufacturers package some of their light-susceptible chemicals, mandelic acid, for example, in black lacquered bottles, which are impervious to light.

Temperature.*—The damaging effect of temperature, even that of the ordinary room, on pharmaceuticals is well illustrated in the case of certain biological drugs. It is important that, in storing and preserving such drugs, their temperatures shall be kept very low. The Pharmacopoeia requires that most of its biologic preparations shall be preserved at temperatures between 2 and 10°C., preferably at the lower limit. It is recommended that smallpox vaccine shall be stored at temperatures below 0°C., for it loses potency rapidly even at a moderately higher temperature. Many pharmacists now have refrigerators in which they store nothing but medicines which are affected drastically by heat. Manufacturers usually place instructions for refrigeration on the labels of drugs needing this protection.

A number of the dermatologic preparations such as ointments made with low-melting fats must be protected against the high summer temperatures prevalent in some parts of the United States. Upon melting, the ingredients of many of these preparations separate. Not only is the esthetic appearance of the substance spoiled, but frequently its therapeutic efficiency is impaired. The Pharmacopoeia permits the addition of high-melting waxes to such preparations as a means of preserving them. Conversely, there are the drugs that freeze or congeal, if not properly stored, during the cold winters of the northern regions. Manufacturers of such substances frequently ask their

*Refer to p. 316, Chap. X.

customers to anticipate their needs and buy early so that the items can be shipped before the cold weather sets in. Some oils such as anise or sassafras will congeal on the pharmacist's shelf during cold nights. When this happens, the Pharmacopoeia directs that the oil shall be carefully warmed at a low temperature until it is liquified and thoroughly mixed before dispensing.

Air.—Air creates a problem in the storage and preservation of drugs, largely because of the oxygen it contains. Air-borne moisture and carbon dioxide are also significant factors, as are certain other substances that occasionally contaminate the mixture. **Arsphenamine** is an example of a widely used therapeutic agent that is susceptible to the action of air. This light-yellow powder quickly becomes darker and more toxic because of oxidation upon exposure to air. The Pharmacopoeia recognizes the situation by requiring manufacturers to store the chemical in sealed colorless glass containers from which the air has been excluded either by displacement with a nonoxidizing gas like nitrogen or by the production of a vacuum.

Tincture of Kino N.F. VII must be stored or preserved in small, tightly stoppered, completely filled bottles. Air will also cause fixed oils to turn rancid. Fats and oils, unless they have been protected by the addition of preservatives such as benzoin in benzoinated lard, rapidly turn rancid because of oxidation. In the process of rancidification, certain "fatty" acids of disagreeable odor and taste are formed. One of these, butyric acid, is largely responsible for the unsavory condition of rancid butter. Since rancid cod-liver oil is neither an appetizing vehicle nor chemically beneficial to the vitamins it contains, the Pharmacopoeia permits the storage of the fresh oil in vacuum-packed containers or in the presence of an inert gas. If ferrous sulfate is not stored so that it is protected from contact with air, several changes may take place. The salt will effloresce in dry air, but on exposure to moist air the crystals oxidize and become coated with a brownish-yellow basic ferric sulfate. The Pharmacopoeia states that when this happens the salt must not be used for any medicinal or official purpose.

Solution of Lead Subacetate N.F. VII is extremely sensitive to the air-borne carbon dioxide, which reacts and causes a white precipitate of lead carbonate to appear in the solution. The

National Formulary therefore directs that the solution should be stored in small, well-filled, tight containers. Air also reacts unfavorably on many of the glandular products such as thyroid, causing such destructive processes as decay, putrefaction, and mold growth.

Age.—Drugs like arsphenamine, neoarsphenamine, solutions of procaine, many tinctures, and fluidextracts deteriorate with age despite any preventive measures used in their storage and preservation. This deterioration factor is so important for many drugs that their makers either voluntarily or at the request of the government place expiration dates on the labels. The substances are not to be used after the expiration dates because of possible impaired potency. Biologicals are outstanding examples of this type of drug.

Chemicals.—Chemicals in contact with the drug either as a part of the formula or as impurities can make its preservation a difficult problem. This is especially true in the case of unwanted impurities that appear either because of contaminated raw materials or because of faulty methods of manufacture. The extemporaneous preparation of certain official ointments furnishes examples in which faulty technique can introduce impurities that make it impossible to preserve the preparation. Ointments of tannic acid, yellow mercuric oxide, and iodine must not come in contact with iron utensils or containers during manufacture or storage. The Pharmacopoeia is specific on this point.

Insects or Small Animal Life.—Vegetable and animal drugs in their crude and even in certain of their processed forms are subject to many types of insect infestation and ravages by small animal life. Dealers in these important substances have a serious problem in preserving their stocks. For drugs of this kind to be "official," they must be substantially free from insects or other animal life, extraneous animal material such as hairs, or animal excreta. In order to protect them from the ravages of insects the Pharmacopoeia directs that, in special cases, they shall be preserved in suitable containers into which is introduced at intervals a sufficient quantity of chloroform, carbon tetrachloride, or some other suitable substance. Other methods for combating these pests are described in books dealing with pharmacognosy.

Fungus or Other Plant Growths.—Plant growths of one kind or another are not uncommon in syrups, in preparations of some organic drugs that are not carbohydrate in character, and on certain plant and animal extracts. These contaminants also appear in the most unexpected places. There is a mold that grows on solutions of arsenic trioxide, which are supposed to be good preservatives and therefore inimical to the growth of unwanted plant life. Sterilization and storage in airtight containers constitute one of the better ways to preserve drugs subject to this type of deterioration. The Pharmacopoeia recognizes the problem in its monograph on Mucilage of Acacia, where it states that the mucilage must not be dispensed if it has become sour or moldy.

Preservative chemicals can often be incorporated into the preparations that are apt to develop molds and bacterial growths. Mucilage of Acacia U.S.P. XII is preserved with 0.2 per cent of benzoic acid, and Syrup of Acacia N.F. VII is protected with 0.1 per cent sodium benzoate. Methyl and propyl *p*-hydroxybenzoates, sold as such and also under trade names such as Tegosept M (methyl *p*-hydroxybenzoate) and Tegosept P (propyl *p*-hydroxybenzoate), are good preservatives. A quaternary ammonium derivative of the pyridine betaine type (Emulsept 607 M) is being used. Many similar products are sold under such names as Moldex, Moldine, and Rancidex. Usually 0.1 to 0.2 per cent of preservative is all that is required to protect either cosmetics or pharmaceuticals from molds, fungi, or bacterial growths.

Volatility.—The vapor pressure of a drug, which is a measure of its volatility, is often a factor in its storage and preservation. Loss of potency need not be guarded against when a pure substance such as camphor volatilizes; the loss here is purely economic, for that which remains is still pure camphor, with all its therapeutic powers retained. However, if the active constituent of a mixture vaporizes, a loss in potency usually results. Containers for storage must be designed to prevent this. Liniments and waters are examples of this volatile class of preparation.

Chemical Stabilizers.—Many drugs are preserved by the addition of small quantities of some chemical that functions as a stabilizer against deterioration. Investigation has shown that

certain solutions are more stable, *i.e.*, they maintain their potency much longer if they are kept at a certain degree of acidity. Manufacturers adjust the hydrogen-ion concentration to produce the optimum acidity or alkalinity and then add buffering chemicals to maintain it; the result is a much more permanent solution. Decomposition is also prevented by the addition of a negative catalyst. The decomposition of solution of hydrogen peroxide is retarded in this way. Traces of acetanilid or acetophenetidin in the solution function here as the retarding catalyst. In this instance, while the Pharmacopoeia makes it permissible to add a preservative it sets an upper limit on the amount (see Limit of Preservative in the monograph on Solution of Hydrogen Peroxide) in order to protect the consumer. Another example of the stabilizing effect of an added chemical is the protective action of sucrose on ferrous salts. Sucrose is used to protect the ferrous carbonate in Mass of Ferrous Carbonate U.S.P. XII and the ferrous iodide in Syrup of Ferrous Iodide N.F. VII against oxidation.

Containers.—Glass, so often called the ideal container material, is responsible for certain difficulties in the storage and preservation of solutions susceptible to decomposition because of contact with alkaline materials. Soft glass, rather than hard glass, is usually the offender, being slightly soluble in many fluids. This is sometimes sufficient to alter the reaction of the solution by increasing its alkalinity. If the therapeutic efficiency is altered by the change in reaction, the solution should be stored in a more resistant glass.

The Pharmacopoeia[1] considers the container sufficiently important to devote several paragraphs to the subject.

The Container.

1. The "container" shall be considered to be the object or objects which hold the drug and which are or may be in direct contact with the drug.

2. The closure of the "container" shall be considered a part of the "container."

3. The "container" shall not interact physically or chemically with the drug which it is holding so as to alter the strength, quality, or purity of the drug beyond the official requirements.

[1] "The Pharmacopoeia of the United States of America," 12th ed., pp. 6–7.

4. A "well-closed container" shall protect the contents from extraneous solids or loss of the drug under the ordinary or customary conditions of handling, shipment, storage, or sale.

5. A "tight container" shall protect the contents packaged from contamination by extraneous solids or moisture, from loss of the drug, and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, or sale, and it shall be capable of tight reclosure.

6. A "hermetic container" shall be impervious to air or any other gas under the ordinary or customary conditions of handling, shipment, storage, or sale.

7. A "light-resistant container" is a container which is opaque, or designed to prevent photo-chemical deterioration of the contents beyond the official limits of strength, quality, or purity, under customary conditions of handling, storage, shipment, or sale.

Unless otherwise directed, a light-resistant container shall be composed of a substance which in a thickness of 2 mm. shall not transmit more than 10 per cent of the incident radiation of any wave-length between 2900 and 4500 Angstrom units, page 570.

If the immediate container in its construction is less than 2 mm. in thickness, the same 10 per cent limit of light transmission shall apply.

If the immediate container in its construction is not light-resistant, it must be provided with an opaque covering, be enclosed in an opaque covering or in an opaque container.

Products packaged in collapsible metal tubes, such as shaving creams, tooth pastes, and ointments, present a problem. Chemicals that react with the material of the tube are sometimes part of the formulas of the contained substances. Corrosion and leakage are the principal visible evidence of such reactions. Tube manufacturers are constantly endeavoring to make corrosion-proof tubes. Tin and aluminum tubes are the most popular in use today.

Tin containers for substances that are already moist, such as hydrous wool fat, or that absorb moisture from the air, such as zinc chloride, are not always satisfactory. Such containers are usually made by plating a thin coating of tin on an iron base. If this protective tin cover is broken, rust spots make their appearance. The substance in the container may then become contaminated with iron.

Plastic containers cause trouble with certain substances. Colored liquids, particularly, if they contain aromatic oils, are apt to stain or spot the plastic material. This makes an unsightly container although the substance is not affected.

Closures.—The closures for bottles and jars should always be selected with a view to the possible reactions between them and the contents of the package. Cork closures, for example, are obviously not suitable as stoppers for bottles containing tincture of iodine or corrosive acids; instead, ground-glass stoppers are clearly indicated. In the case of the tincture, rubber closures are also acceptable. There are occasions where cork stoppers covered with paraffin or tin foil are satisfactory substitutes. The Pharmacopoeia gives directions for the preservation of chloroform in bottles closed with cork stoppers provided that these are covered with tin foil or other suitable material. Bottles holding the official solution of hydrogen peroxide may be closed with cork stoppers that are coated with paraffin. Similar stoppers are also mentioned in the Pharmacopoeia as satisfactory for bottles containing sodium or potassium hydroxides. This reference states, regarding the storage of iodine, that the chemical should be preserved in glass bottles closed with stoppers resistant to corrosion.

Plastic closures frequently have either an inner waxed-paper lining or one of foil. Many substances soften, corrode, or discolor them. The lacquered tops of jars for ointments or creams are often marred because the material enclosed eats away the lacquer. Some fatty substances that are perfectly harmless to the skin are particularly active in this respect.

Fire.—A most important factor in the problem of the storage and preservation of some drugs is fire. Too many pharmacists fail to consider its significance. Yet the Pharmacopoeia calls attention to the hazard a number of times and directs that the following should be stored in places remote from fire: acetone, collodion, ether, ethylene, petroleum ether.

Package Size.—The Pharmacopoeia has limited the maximum size of the package permitted for several official substances. This was done because of their rapid deterioration and the fact that they are infrequently called for in trade. The substances are apomorphine hydrochloride, 0.35-Gm. package; paraldehyde,

120-Gm. package; physostigmine salicylate, 1-Gm. package; and sulfurated potash, 120-Gm. package.

Sterilization.—Another difficult problem facing the manufacturer and dispenser of drugs is that of preserving certain medicinals in sterile form. A discussion of the techniques for accomplishing this belongs in works devoted specifically to the subject.* The concern of the Pharmacopoeia over proper maintenance of sterility when it is necessary is demonstrated in the monograph for Normal Saline Solution. According to this, the solution must be protected from contamination and should be used within 24 hr. after its sterilization if not stored in hermetically sealed containers. The Pharmacopoeia also states that purified solution of liver must be sterile and may contain not more than 0.5 per cent of cresol or phenol. The cresol and phenol are used as a chemical means of maintaining sterility.

Research.—In the past, research on the storage and preservation of drugs has not kept pace with other phases of pharmaceutical manufacture; however, future activity in the field is almost certain to be great. While much of the work is chemical in nature and has to do with the effect of chemical stabilizers as preservatives, considerable work is being done on protective packaging. The packaging of drugs and cosmetics has progressed in recent years along several important lines. Progress has been made in increasing the effectiveness of the container as a preserver of its contents, all the factors discussed in this chapter, such as the deleterious effect of light and moisture, being taken into consideration. The effect of the appearance of the container on the consumer has been seriously studied; apparently some designs subconsciously impress the users more favorably with respect to the value of the contents. Research is being done in a constant effort to improve containers from the point of view of ease of removal of the contents, conservation of shelf space, and general utility. Some of the larger manufacturers of containers as well as pharmaceutical manufacturers maintain research divisions whose principal function is to study the difficult packaging problems of their customers.

* See Chap. XII for a more lengthy discussion of processes of sterilization.

STUDY QUESTIONS

1. What are some of the factors known to cause the deterioration of drugs?
2. What chemical is used to preserve solution of hydrogen peroxide?
3. Why are many biologic drugs stored in a refrigerator?
4. Why must ephedrine be stored so that it will be protected from moisture?
5. Why do certain ointments present a storage problem in summer?
6. Explain how vapor pressure can become an important factor in storage.
7. Under what conditions are tin containers unsuited for drugs?

COLLATERAL READINGS

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CHAPTER XX

THE NATURAL PRODUCTS USED IN PHARMACY

It behooves the pharmacist to be as careful as possible about the products he uses in the practice of his profession. Many of the laity are somewhat informed about drugs, and pharmacists cannot afford to know less about drugs than their customers. No pharmacist can be familiar with all the countless numbers of drugs. But he must be sufficiently well informed to satisfy inquiring customers; otherwise, he will lose their confidence.

To be an intelligent practitioner, the pharmacist must retain certain facts about many items. There are countless new medicinals appearing upon the market almost daily, too many for anyone to remember them all. The general classes of natural products include celluloses, starches, sugars, gums, mucilages, resins, oleoresins, gum resins, balsams, fats, volatile oils, hydrocarbons, alcohols, organic acids, alkaloids, glucosides, neutral principles, ferments, and enzymes. Serums, bacterins, vaccines, hormones, and vitamins may also be included.

Acacia is a common pharmaceutical item. It is not sufficient to know that it is an emulsifying agent and an adhesive; the pharmacist should know that it is a gum and a product of exudation. He should also understand its general physical properties, keeping qualities, and uses.

The classes of substances that have been named are, with few exceptions, complex compounds. They may be truly termed natural products of plants or animals obtained, not spontaneously, but only after subjecting the natural product to some sort of processing. A good example of this is Terebinthina, crude turpentine, which is described as a concrete oleoresin. The pine tree produces this in a natural way, but it is obtained usually as the result of an injury to the tree. The crude turpentine exudes at the site of the injury. By further processing in the form of distillation the crude turpentine may be made to yield oil of

turpentine, commonly known as "turpentine" or "turps," and resin or rosin; each of these drugs is complex and may further be broken down.

While the exact chemical composition of many of these natural plant products remains unknown, information about them is accumulating. We know now that some of the old names are misnomers. For example, **balsam of copaiba** is not a **balsam** but an **oleoresin.** In the same way we talk about **gum benzoin** and **gum opium,** neither of which is a gum. Other illustrations could be given.

A brief study of these important classes of natural drug products will now be made in an effort to acquaint the student with the nature and character of those substances which are used so often in preparing the official galenicals and in dispensing practice. The following discussion centers in the characteristics of the group under consideration, but some of the dispensing and manufacturing problems involved in the use of certain of the members in each class will also be pointed out.

CELLULOSE

Living cells are surrounded by a cell wall, from which cellulose may be derived. The purest form of cellulose available to us is **Gossypium purificatum** or the official **cotton,** known as absorbent cotton.

Cotton is the hair of the seed coat of cultivated varieties of the cotton plant, *Gossypium herbaceum.* It consists of long filaments, each of which is a single empty cell. The mature fiber is more or less flattened and upon being examined under the microscope appears to be somewhat twisted. The microscopic characteristics are then, in addition to the twist, a canal, cell walls, and particles of dried cell content.

The cotton fibers are removed from the seeds by the process of ginning. Raw cotton fibers have a thin coating of wax and oil rendering them impervious to water. In this condition cotton is nonabsorbent and floats because of the fact that the water cannot penetrate the cell and replace the air in the lumen. Clean nonabsorbent cotton serves very well for plugging culture flasks but is useless as a surgical dressing.

Cotton is rendered absorbent by boiling in an alkaline solution for several hours, which saponifies the wax and fat. It is next washed thoroughly with water and bleached with a weak solution of chlorinated lime. Following this treatment, it is washed with a diluted solution of hydrochloric acid, rinsed thoroughly in pure water, dried, and carded. It may lose as much as 10 per cent in weight during this process. The student is referred to the Pharmacopoeia for the **description,** the **physical properties,** and the **tests for identity of cotton.**

Absorbent cotton, or **cotton wool,** is soluble in strong alkalies, strong sulfuric acid, and ammoniacal copper oxide solution. As a mechanical agent it has many uses in pharmacy for such operations as filtering, straining, and stoppering. It has value in surgery as a dressing because of its absorbent power.

Pyroxylin, known as **soluble guncotton,** is obtained by treating cotton with a mixture of nitric and sulfuric acids. It is composed chiefly of cellulose tetranitrate, which is soluble in a mixture of three parts of ether and one part of alcohol forming **collodion.** It is soluble also in acetone and glacial acetic acid, is inflammable and explosive, and should be handled and stored with care.

Cotton may be medicated by impregnating it with a solution of the medicinal agent, then expressing and drying it. Antiseptic gauzes medicated with such chemicals as boric acid, iodine, mercury bichloride, iodoform, and similar products are available. More important, perhaps, is the fact that cotton is used to prepare absorbent gauze, which may be medicated with any one of a number of antiseptic chemicals. Muslin, which is heavier cotton cloth than gauze, may be impregnated with dried calcium sulfate and used for bandages.

Rayon, celanese, lustron, viscose, and other terms are names for **artificial silks,** which are obtained by careful chemical treatment from cotton and other forms of cellulose. The fact that cellulose is soluble in strong alkalies and ammoniacal copper oxide makes it possible to prepare the so-called "artificial silks."

It is possible to obtain **dextrin** from cellulose by treating the latter with strong sulfuric acid. Other useful products obtained from cellulose by chemical treatment are paper, filter paper, parchment paper, lacquers, cellophane, and film material.

The celluloses have been classified by Onslow[1] as follows:

1. Normal celluloses.
2. Compound celluloses.
   a. Lignocelluloses.
   b. Pectocelluloses.
   c. Adipo- or cutocelluloses.
3. Pseudo- or reserve celluloses.

STARCHES

Starch is one of the most interesting and useful of all the natural plant products. It has no medicinal virtue but is important as a food. It has a few good pharmaceutical uses, but its presence in certain drugs is often a cause of trouble.

Starch is manufactured in the green leaves of plants from carbon dioxide and water under the influence of chlorophyll. Man has not been able to unravel nature's secret in the production of this important economic item, which occurs chiefly in the seeds, roots, and rhizomes of plants. Foods such as the cereals, flour, potatoes, and products prepared from them are composed essentially of starch. Starch is insoluble in cold water, alcohol, glycerin, weak acids, and weak bases. However, when treated with boiling water it breaks down into a gelatinous paste that is more or less soluble.

As it is obtained from plants, starch exists in the form of granules. These are microscopic in size and characteristic in size and shape for each plant, making it possible to identify the source of the starch by means of the microscope. The granules of rice starch are the smallest of those of the common starches, and for this reason rice starch has been used in face powders. **Amylum** (corn starch) is official and is larger than rice starch. Potato-, wheat-, and tapioca-starch granules are much larger, in fact, are among the largest of those of the well-known starches. The granules have a very hard outer coat, which is ruptured by boiling or prolonged trituration. This fact makes it possible to prepare starch paste and glycerite of starch.

Starch has a strange affinity for water. Air-dried starch contains about 14 per cent of water. If made anhydrous, it absorbs the same amount of water with the evolution of heat.

[1] M. W. Onslow. "Practical Plant Biochemistry," Cambridge University Press, London, 1929.

In absorbing water the starch swells. This makes dry starch an excellent disintegrating agent for compressed tablets. It is used as an absorbent and dusting powder. Upon being heated for a period of time at about 200°C., starch is converted into **dextrin.** This reaction may be accelerated at a lower temperature by the addition of sulfuric or nitric acid, the end product being **dextrose.** Starch may also be hydrolyzed to **dextrin,** to **maltose,** and, finally, to **dextrose** by **diastase,** the active enzyme of malt. Starch is valuable as a food because it can be hydrolyzed to **sugar** by amylolytic enzymes.

Chemically, starch is classed as being similar to cellulose, which is represented by the formula $(C_6H_{10}O_5)_n$. **Inulin,** found in **Taraxacum,** and **lichenin,** occurring in **Cetraria,** are closely allied to starch and are isomeric with it as to composition. Starch paste gives a blue color with iodine solution. Lichenin and inulin paste develop a yellow color with iodine solution. **Glycogen,** which is found in the livers of animals, is said to be a modification of starch.

GUMS

Gums are amorphous, transparent, or translucent plant exudates or, in some cases, excretory products. They are classed as **carbohydrates** and exhibit mucilaginous properties. They may be glucosidal inasmuch as some can be hydrolyzed to sugars and acids of high molecular weight. Upon oxidation with nitric acid they yield **mucic acid.** By the same treatment starch yields dextrin.

Solutions of gums are adhesive and serve as good suspending and emulsifying agents. They may be precipitated from aqueous solutions by strong alcohol and by solutions of heavy metal salts. Lead subacetate solution is said to be the most delicate reagent for gums. True gums consist largely of **arabin,** or **arabic acid,** in combination with calcium, potassium, and magnesium.

Gum arabic, or **acacia,** is the most widely used of the natural gums. It comes from the Mediterranean area, as do many other exudate drugs. Arabin, or arabic acid, may be hydrolyzed from mucilage of acacia by means of hydrochloric acid and subsequent precipitation with alcohol. However, it will not dissolve in water until limewater or some other alkaline solution has been added.

Metarabin, or **cerasin,** is the insoluble portion of **cherry gum.** It exudes upon peach, plum, and cherry trees and may be prepared from acacia by heating the latter to 120 to 150°C. Acacia so treated does not dissolve in water but absorbs it and swells.

Parabin, which is said to be isomeric with arabin, is a constituent of **Agar.** It also swells in water, is soluble in dilute acids, and in turn is precipitated by alkalies.

MUCILAGES

It is not unusual to think of gums and mucilages as a general class of plant products. Some authorities make a distinction between the two in respect to their behavior toward water. Gums are considered to be soluble, while the mucilages merely swell in water. Acacia is an official example of a gum. In the same way, tragacanth is a mucilage because, while it does not go into solution, it does swell and form a gel. Like gums, mucilages are colorless, odorless, amorphous, and partly insoluble substances. They form sticky translucent gels with water and are more soluble in alkaline solutions.

The chief constituent of tragacanth is called **bassorin,** an insoluble pectinlike substance. The soluble portion (8 to 10 per cent) of tragacanth is regarded as a true gum although it is not precipitated by alcohol or lead subacetate.

Tragacanth has long been an important constituent of hand lotions. Inasmuch as it is insoluble, such lotions are usually not clear and are often quite thick. **Mucilage of tragacanth** (Mucilago Tragacanthae U.S.P. XII) serves as an excipient for pill and troche masses. In the form of a gel, tragacanth has been the chief component of surgical lubricating jellies. Both mucilage of acacia and mucilage of tragacanth are good media for the growth of molds. Benzoic acid in the concentration of one-tenth of 1 per cent is permitted to be added to mucilages for its preservative action. This concentration is not adequate for any length of time. The addition of a slight excess of chloroform serves the purpose of preservation satisfactorily and does not interfere with the pharmaceutical uses of the preparations in any way.

The mucilaginous constituent of Irish moss (Chondrus N.F. VII) is called **carragheen.** Chondrus is much more soluble in water than tragacanth and is not precipitated by alcohol. It serves

as an emulsifying agent and is preferred in some instances to acacia or tragacanth. It forms a clear, viscid liquid when boiled in the ratio of one part to about thirty-five parts of water. It has some uses as a hand-lotion ingredient.

AGAR

Agar is the dried mucilaginous substance obtained from certain marine algae, found along the tropical coast of China and the coast of California. It has been referred to as the most powerful gelatinizing agent. It is insoluble in cold water and is soluble in boiling water but forms a gel upon cooling when even as dilute as 1 part in 100. It is obtained in bundles of thin, membranous pieces or in granulated form. It is stable when dry but spoils readily when moist, serving as a medium for the growth of molds and bacteria and having wide use in culture media for bacteriological work. It is used as a laxative, being largely mechanical in action. Agar has some value as an emulsifying agent.

The chief constituent of agar is **gelose,** a carbohydrate that may be hydrolyzed to **galactose.** Diatoms may be found in the ash. A solution of agar does not form a precipitate with picric acid test solution, a fact that distinguishes it from gelatin.

PECTINS

Pectins are nonnitrogenous gumlike substances widely distributed in plants. Green unripe fruits contain **pectose,** which may be isomeric with cellulose and gives hardness to them. The presence of an enzyme, **pectase,** aided by heat, sunlight, and organic acids, causes fruits to ripen. The **pectose** is changed to **pectin** or **pectosic acid.** This type of reaction accounts for the gelatinization of certain fruit juices, such as cherry and raspberry, and pharmaceutical preparations of senega, taraxacum, and other root drugs. Ammonia water or other alkalies may be added to pharmaceuticals to prevent gelatinization because they form soluble compounds with pectin and pectosic acid. A good example is the use of ammonia water in fluidextract of senega (Fluidextractum Senegae N.F. VII).

In preparing syrups of cherry and raspberry from the respective fruit juices the latter are allowed to stand for a few days to per-

mit the pectinaceous bodies to be removed by fermentation. This clarifies the juices.

SUGARS

Sugars, starches, gums, mucilages, and celluloses are classed as carbohydrates and are important to the life of plants. Sugars include a large class of carbohydrates described as white, odorless, crystalline, soluble in water, and more or less sweet to the taste. Dilute solutions of sugars are easily fermented. Concentrated solutions are stable and act as preservatives. This is illustrated in the official syrups, which are stable.

Sugars are conveniently divided into two groups, namely, **monosaccharides** and **disaccharides.** A third group of carbohydrates known as the **polysaccharides** includes the starches, gums, mucilages, and celluloses. These are not sweet to the taste but may be made to yield simple sugars by being boiled with dilute acids and by other means.

The relationships of the commonly known carbohydrates may be clarified by the following outline.

1. Monosaccharides (monoses).
   a. Trioses—$C_3H_6O_3$, glycerose.
   b. Tetroses—$C_4H_8O_4$, erythrose.
   c. Pentoses—$C_5H_{10}O_5$, arabinose, xylose, rhamnose.
   d. Hexoses—$C_6H_{12}O_6$, dextrose, levulose, galactose, and others.
2. Disaccharides (dioses).
   $C_{12}H_{22}O_{11}$, sucrose, lactose, maltose, and others.
3. Trisaccharides.
   $C_{18}H_{32}O_{16}$, raffinose, and others.
4. Tetrasaccharides.
   $C_{24}H_{42}O_{21}$, stachyose.
5. Artificial sugars of these and other groups which have been synthesized.
6. Polysaccharides (nonsugars).
   a. $(C_6H_{10}O_5)_n$, starches, dextrin, inulin, glycogen, etc.
   b. Gums, acacia, etc.
   c. Mucilages, tragacanth, etc.
   d. Pectins, pectin, etc.
   e. Celluloses, $(C_6H_{11}O_5)_n$, cotton, etc.

Monosaccharides

Monosaccharides are those sugars which cannot be further simplified by hydrolysis. They may be regarded as **aldehydes** and **ketones** derived from their respective alcohols. They do

not all contain the same number of carbon atoms. Of this group only the **hexoses,** chiefly dextrose, are of much interest to the pharmacist.

Dextrose U.S.P. XII is to be found closely associated in nature with **fructose** of fruits and in honey. It is prepared by treating **corn starch** with diluted sulfuric acid. This process changes the **starch** into **dextrin** and then into **dextrose.** The liquid portion, or Syrupy Glucose U.S.P. XII, usually contains unconverted dextrin. The solid portion, or grape sugar, represents complete conversion to dextrose.

The student is referred to the Pharmacopoeia for a more complete description of dextrose or *d*-glucose. It is used in medicine, as a reagent, and, sometimes, as a food. Ampuls of dextrose and of dextrose and sodium chloride are extensively used.

Solutions of dextrose are easily fermentable. Dextrose is a reducing sugar and may be determined quantitatively by boiling it with a volumetric alkaline solution of cupric tartrate (Benedict's volumetric solution). The dextrose reduces the cupric tartrate solution, causing it to yield greenish, yellowish, or reddish cuprous oxide, depending on the degree of reduction.

Glucose U.S.P. XII, or **Liquid Glucose,** is the product of incomplete hydrolysis of starch. As such it is composed chiefly of dextrose, maltose, and dextrins in addition to water. It is a thick, syrupy liquid with a specific gravity of 1.54. It is miscible in all proportions with alcohol and water, contains reducing sugars, and has limited uses in pharmacy. For details relating to the description and tests for identity and purity, the reader is referred to the monograph on Glucosum Liquidum in the Pharmacopoeia.

Levulose, or **fructose,** is found in honey or in fruits, associated with dextrose. In the latter instance it is known as **fruit sugar.** It bears the name **levulose** because it is levorotatory. It is a yellowish syrup, very sweet, and crystallizes with difficulty. It is described as the liquid portion of honey, the granular portion being dextrose.

Honey (Mel U.S.P. XII) is a mixture containing 65 to 80 per cent of the sugars dextrose and levulose, 20 to 30 per cent water, and 0.1 per cent formic acid. The latter is presumably a pre-

servative agent that is driven off when the honey is heated for clarification and straining.

Invert sugar is a term that is often given to a mixture of fructose and dextrose. It may be formed by the inversion of cane sugar by heating the latter with acids or by the action of certain ferments.

Disaccharides

The two important official disaccharides are **sucrose** and **lactose.** They are each given the general formula $C_{12}H_{22}O_{11}$ because they represent, chemically, a combination of two molecules of a monosaccharide with the elimination of a molecule of water ($2C_6H_{12}O_6 \rightarrow C_{12}H_{22}O_{11} + H_2O$). The disaccharide molecule may be made to break up into two monosaccharide molecules by the action of heat, water, and dilute acids.

There are other members of this group, the most important of which is **maltose.** Excepting maltose, the disaccharides cannot be fermented without first being inverted into one or more of the monosaccharides.

Sucrose is a colorless, white, crystalline sugar obtained from sugar cane or the sugar beet. It is odorless, the sweetest of all sugars, and stable. It is sometimes reduced to a powder, to which is added a small amount of starch and is then known as *confectioners' sugar.* When made to crystallize in large prisms, it is known as *rock candy.*

In the manufacture of sugar, the juices of the sugar cane and the sugar beet are treated with lime to neutralize the acids present and aid in clarifying them. The lime is removed by treatment of the mixture with carbon dioxide gas. The juice is concentrated under vacuum and then evaporated until crystallization occurs. The syrup is removed from the crystals by centrifugal machines and is then known as **molasses.**

The raw sugar crystals are dried by this process and refined by dissolving them in water, followed by clarification and filtering. Decolorization is effected by passing sugar solutions through bone-black filters. The clear solution is again concentrated under reduced pressure, forced to crystallize as small granules, and dried by centrifugal machines. The raw beet sugar is more difficult to refine than the cane sugar. Ultramarine blue was

formerly used to whiten the sugar in preference to clarification by bone black. Syrups made from sugars that were whitened by ultramarine were usually slightly yellowish.

Sucrose is soluble in about one-half its weight of water at laboratory temperature. **Syrupus** U.S.P. XII is nearly a saturated solution of sucrose at 25°C. It has a specific gravity of 1.31 and contains about 65 per cent of sugar by weight.

Sugar, upon being heated to about 180°C., yields a product known as **levulosan.** Above 205°C. it forms a dark, brown, thick, bitter liquid of a complex nature known as **caramel,** which is official in the National Formulary and is used chiefly as a coloring agent. Diluted sugar solutions may be hydrolyzed to invert sugar by heating. The action is much more rapid in the presence of a diluted mineral acid. Yeast or other ferments may cause the same change. Sucrose is dextrorotatory, and this property is a means of determining its purity.

Sugar and syrup are valuable preservatives and useful as adjuvants and sweetening agents in pharmacy.

Lactose U.S.P. XII is "sugar of milk" and may be prepared by adding hydrochloric acid to milk to precipitate the casein. The casein is filtered off and the whey treated with lime, which coagulates the albuminous matter. The treated liquid is then filtered through charcoal to clarify it and set aside to crystallize. Lactose is present to the extent of about 3 to 6 per cent in milk and, as usually obtained, contains one molecule of water.

In the process of being crystallized, if the solution of lactose is heated to 93.5°C. the ordinary **α-lactose** is changed to **β-lactose.** The latter is said to be sweeter and more acceptable pharmaceutically for that reason. The β form is said to be an anhydride, while the α form is usually a monohydrate.

Sugar of milk is usually in the powder form and gives the sensation of grittiness between the teeth. It is hard and odorless, is soluble in about five parts of water, is dextrorotatory, and reduces Fehling's solution (sucrose will not). It may be hydrolyzed to yield **dextrose** and **galactose.**

Lactose should be free from dextrose, sucrose, dextrin, and starch. It is important medicinally as a constituent of baby foods and pharmaceutically as a diluent, being harmless and nonabsorbent. Like sucrose it has been synthesized but is a

product of the milk industry. Details concerning its properties and tests for purity may be found in the Pharmacopoeia.

Maltose is the sugar obtained from **malt.** Malt is barley that has been moistened and put in a warm place until it begins to sprout and then heated sufficiently to kill the young plants. During this process the diastase of malt, acting upon the starch, forms maltose. By means of diastase, yeast, or dilute acids it is possible to split maltose into two molecules of dextrose. In the manufacture of maltose on the commercial scale, germination of the barley is allowed to proceed until all the starch has been converted to maltose. Diastase is a good example of the function of an enzyme in the germination of seeds (see Extractum Malti U.S.P. XII). Maltose is soluble and strongly dextrorotatory.

Honey is a saccharine secretion manufactured by the bee and deposited in the honeycomb. It is of plant origin, inasmuch as the bee makes it from nectars that are extracted from flowers.

Honey is one of man's oldest foods and medicinal products. It is a good vehicle for sweetening and disguising purposes. It has also been credited with many medicinal virtues that cannot be easily substantiated. **Clarified honey** was official in the Pharmacopoeia for a considerable period of time. Pure honey is now separated from the comb by centrifugal means and is a clear, clean, pure product. For this reason **Mel,** pure honey, replaced **Mel Depuratum** in U.S.P. XI. It is a nearly saturated solution of dextrose and levulose with traces of volatile oils, cane sugar, dextrin, and formic acid. It keeps well, unless diluted with water; varies in appearance from a viscid colorless to a brownish-yellow liquid; and is a good food.

RESINS

Resins are solid plant principles, amorphous, fusible, inflammable, and brittle. They are soluble in alcohol, ether, and chloroform; some are soluble in fixed and volatile oils; and all are insoluble in water. They are acidic and therefore react with alkaline solutions to form resin soaps. **Rosin** U.S.P. XII is an example of a resin. The cheaper laundry soaps in times past often had a decided resinous odor.

As a class of natural plant principles, it may be said that less is known about resinous products than almost any other group

of substances. It is interesting that nearly all the official resins are constituents of compound cathartic pills. They are active in small doses. The cathartic activity of each resin is attributed to the presence of **glucosides.** For instance, **scammonin** is the glucoside to be found in resin of scammony. Resin of jalap is about 90 per cent **convolvulin.** Resin of podophyllum is complex. Its cathartic action is attributed to podophyllotoxin, which comprises about 50 per cent of the product and is quite active as a purgative.

Resins usually occur in plants combined in some way with fixed oils, volatile oils, and gums and perhaps with acids such as tannic acid. In composition they may be organic acid esters, compound ethers of certain alcohols, or possibly anhydrides. Rosin is composed chiefly of abietic anhydride. Certain resinous products are plant exudates such as myrrh and asafetida. These are examples of **gum resins.** When triturated with water, emulsions or milklike products result, the albuminous matter serving as a suspending agent for the insoluble resinous material. Emulsion, or milk, of asafetida has long been known.

Resins are secretions. Rosin, which is obtained, by distillation, from the concrete oleoresin secreted from *Pinus palustris* and other species of pine, is a good example. Most of the official resins are obtained by extracting such crude drugs as scammony, ipomoea, jalap, and podophyllum. In some cases resins may be produced by the oxidation of volatile oils.

Resins and resinlike products are to be found widely distributed in the plant world although only a few are of medicinal importance. In addition to the resins of the crude drugs already mentioned, there are others such as **guaiac resin** and **mastic.** Burgundy pitch, which is no longer official, is a resin prepared from certain species of the fir. Synthetic resins are of technical importance.

For details concerning the origin, description, and properties of official resins, the student is referred to the Pharmacopoeia, the National Formulary, and other sources.

OLEORESINS

Oleoresins are, with one exception, liquid preparations obtained by extracting the drugs with appropriate menstruums,

usually alcohol, ether, or acetone. Following the extraction, by the percolation procedure, the percolate is concentrated by distillation or evaporation. The oleoresins that remain are concentrated liquids, with distinctive odor, color, and taste.

As the name implies, oleoresins are natural mixtures of resins with volatile and fixed oils. They have properties common to their chief components, *i.e.*, they are insoluble in water but soluble in alcohol and other organic solvents. Their odor is attributed to volatile oils, which, if removed, leave a resinlike residue.

The exception to the general definition of oleoresins is that of crude turpentine (terebinthina), which is defined as a **concrete** oleoresin. It is called white turpentine and is a secretory product obtained from *Pinus palustris* or other species of pine. It exudes from the injured tree as a viscid liquid, which dries upon exposure to a hard residue. When this is subjected to distillation, the volatile oil of turpentine is removed and the residue is *rosin*, which is mentioned under resins.

The official oleoresins, in addition to crude turpentine, are **aspidium, capsicum, cubeb,** and **ginger.** Others, which have been official in the past, are **lupulin, parsley fruit,** and **pepper. Copaiba** is official and is an oleoresin but is not so listed. It is referred to as balsam of copaiba, which is a misnomer.

While there are no official strengths assigned to oleoresins, they are much stronger than the crude drugs from which they are derived. They are the most concentrated of our liquid pharmaceuticals.

GUM RESINS

Gum resins are plant exudates composed, as the name implies, of mixtures of gums and resins. They exist in the plant as adhesive, milky juices, which exude at the places where the plants are cut or injured. The exudate is allowed to dry spontaneously and is gathered as a dry product. There is a considerable variation in the proportion of gum and resin in gum resins. Even different samples of the same gum resin vary.

The two outstanding gum resins are myrrh and asafetida. Their behavior toward water has been described under Resins. The activity of the gum resins is attributed to their resin con-

tent. Official tinctures are prepared from myrrh and asafetida. The constituents of asafetida are listed as about 30 per cent gum and 63 per cent resin in addition to a small amount of volatile oil and other substances. Myrrh is composed of about 60 per cent gum, 30 per cent resin, and 6 to 7 per cent volatile oils. Each has a characteristic odor. Other gum resins are **ammoniac, galbanum,** and **gamboge.**

BALSAMS

Balsams are sometimes referred to as odorous resins or oleoresins; they differ from the true oleoresins in the presence of cinnamic and/or benzoic acid, or the esters of these, or even both. The presence of these acids not only imparts odor but gives balsams their value as preservatives. It is for these reasons that lard is benzoinated with Siam benzoin.

The balsams are insoluble in water but soluble in alcohol, ether, and chloroform. The so-called "balsamic," or "odorous," principles may be removed from the crude drugs by sublimation or by means of hot water or hot fats. Examples of resinous balsams are **benzoin** and **tolu. Storax** and **Peruvian balsam** are of the oleoresinous variety.

Botanical origins, descriptions, physical properties, and tests for purity may be found in the Pharmacopoeia and National Formulary for those which are official.

FATS

Fats are glycerides, or esters, of fatty acids. They are formed by the reaction of glycerol, a trihydric alcohol, and fatty acids.

In pharmacy, it is customary to refer to fats as **fixed fats** and **oils,** the fats being solid or semisolid, while the oils are liquid. Fats are chiefly of vegetable origin, although a few important ones are animal products.

When pure and fresh, fats are colorless, odorless, tasteless, and neutral in reaction. On the other hand, most fats have a characteristic odor and color. These qualities are attributed to certain impurities, which become more pronounced with age. The development of odors in fats is due, perhaps, to oxidation of the

impurities and some of the fat as well; in either case the odorous volatile fatty acids are produced, this condition being commonly known as **rancidity.** Fats in general become rancid upon standing, especially if exposed to air and moisture, and may vary greatly in the degree of rancidity developed upon exposure. This is a characteristic quality of the oil. Inasmuch as rancidity is due to the presence of fatty acids, the fats may be made sweet again by washing with weak solutions of alkalies. Rancid butter may be renovated or made sweet again by this washing process. In the final steps of butter renovation salt is worked in to replace that which was removed in the washing. Processed, or renovated, fats are more prone to oxidation than the original fats. Only fats free from rancidity should be used in pharmacy since the fatty acids in rancid fats might prove irritating to tender skins if used in ointments and liniments. Rancidity may be retarded by keeping fats in a cool dry place, in well-filled containers away from the light.

Plant fats are mostly liquid, although one, **oil of theobroma,** is a solid at ordinary temperature. Fats and oils are insoluble in, and lighter than, water and are soluble in ether, chloroform, carbon tetrachloride, petroleum benzin, and carbon disulfide. Castor oil is soluble in alcohol up to an equal amount of each. All fats are greasy to the touch and produce a greasy stain upon paper that does not disappear upon standing.

The **volatile oils,** which are quite different chemically, do not leave permanent stains when dropped upon paper and allowed to evaporate. Fixed fats and oils are not inflammable but will burn, by the aid of a wick, producing a smoky flame. The solid fats readily liquefy at moderate temperature, and the liquid fats under like conditions become more fluid. When subjected to high heat, fats will produce **acrolein,** which is **acrylic aldehyde,** a very irritating compound.

Much attention has been given to the stabilizing of fats and oils, *i.e.*, the prevention of rancidity by chemical agents. These substances are termed **antioxidants,** and many are phenolic in character. Their use in edible oils may well be questioned. Perhaps the best example of this is the treatment of lard with Siam benzoin. The powdered benzoin is allowed to macerate in the melted fat for about two hours and is then removed by

straining. The acids of benzoin serve to retard the development of rancidity and add odor to the lard.

Fixed oils and fats are obtained from their natural sources by the following methods: (1) expression; (2) separation, in which the ground material is mixed with warm water and the oil floats out on top and is drawn off; (3) extraction, in which the oil is dissolved out by the proper volatile solvents and the latter are removed by distillation or evaporation. Crude oils so obtained are then subjected to processes of refining, including clarification and filtering, because they contain mucilaginous and albuminous impurities pressed out with the oil.

Fixed oils are often bleached by treating them with such agents as hydrogen peroxide, chlorine, sulfurous acid, and other bleaching chemicals. Hydrogen peroxide is said to be the agent in greatest favor for this purpose.

Animal fats are obtained by heating the fatty tissues of the animals, including the leaf lard of the hog, over a low flame and straining to remove particles of membranous tissue. This process is commonly referred to as **rendering.**

Certain of the fixed oils, upon oxidation, thicken and finally solidify. If spread out in thin layers, they form varnishlike thin coatings and are known as **drying oils.** Such oils are useful in paints; linseed oil is the one commonly used, although oils of cottonseed, poppyseed, and hempseed and tung oil have this property. The other oils are nondrying oils. The drying or nondrying property of oils may be determined by their behavior with sulfuric acid; the drying oils always show the greatest increase in temperature when mixed in the proportion of 5 Gm. of oil to 1 cc. of the acid. From these properties it is clear that drying and nondrying oils behave differently toward oxygen. This is attributed to the fact that the nondrying oils are saturated, while the drying oils are unsaturated. For this reason, they react differently upon oxidation.

Most fats and oils are composed of two or three compound esters, known as **olein, palmitin,** and **stearin.** Olein is always liquid and is the chief constituent of the liquid fats. Palmitin and stearin are solid at ordinary temperature and are to be found in the solid fats such as lard and tallow. These three are fatty acid esters of glycerin, known as **glyceryl trioleate** ($C_3H_5(C_{18}$-

$H_{33}O_2)_3$), **glyceryl tripalmitate** ($C_3H_5(C_{16}H_{31}O_2)_3$), and **glyceryl tristearate** ($C_3H_5(C_{18}H_{35}O_2)_3$). Most fats are composed of mixtures of these esters and are not simple chemical compounds.

The Pharmacopoeia and the National Formulary have adopted four general tests for fats that depend upon their reactions with potassium hydroxide and iodine. These are (1) acid value, (2) ester value, (3) saponification value, and (4) iodine value. The student is referred to these texts for details.

The common fats of animal origin are lard, suet, wool fat, and cod- and other fish-liver oils. Those of vegetable origin are castor, chaulmoogra, almond, linseed, corn, olive, sesame, theobroma, cottonseed, croton, and other oils.

WAXES

Waxes should be discussed in connection with fats because they have pharmaceutical uses in common and are of a similar chemical structure. Fats have been defined as glyceryl esters of the higher fatty acids. Waxes are esters of fatty acids with high molecular-weight alcohols instead of glycerol. Cetyl alcohol ($C_{16}H_{33}OH$) is an example.

The official waxes include **yellow wax, white wax,** and **spermaceti.** Yellow wax is well known; it is a concrete substance prepared by the honeybee and made into the comb, in which honey is stored. When freed from honey, which is usually done by centrifuging, the comb is washed, melted, strained, and made into small cakes. It is a yellow solid, with a pleasant, aromatic odor. It melts at about 62°C. and has a specific gravity of about 0.95. Since it is official, there are tests for determining its identity and purity, but these need not be given here.

Beeswax is composed chiefly of three substances, namely, (1) **myricyl palmitate,** (2) **cerotic acid,** and (3) **cerolein.** These three may be separated from wax by proper treatment with boiling alcohol and cold alcohol.

White wax is bleached by exposing it to the action of air, light, and moisture. The complete removal of color may require the process to be repeated more than once. When the bleaching is completed, the wax is melted and cast into cakes.

Spermaceti (Cetaceum U.S.P. XII) is a waxy substance obtained from the head of the sperm whale. It is composed chiefly of cetyl palmitate and is a translucent solid that breaks with a scaly fracture. It has a specific gravity of about 0.93 and melts between 40 and 50°C. It is a constituent of cold creams and is used as a hardening agent in ointments.

Synthetic **cetyl alcohol,** is obtained from certain vegetable oils and has largely replaced the natural product for pharmaceutical purposes. It is an important constituent of the so-called "water-absorbing" ointment bases.

Other waxlike products of pharmaceutical importance and interest are **paraffin,** a mixture of solid hydrocarbons obtained from petroleum, and **ceresin,** an impure paraffin. Synthetic waxes, such as the "carbo-waxes," because of their behavior toward water, are attracting considerable attention but have not come into use in pharmacy as yet.

VOLATILE OILS

The odors of plants are attributed to the presence of **volatile oils,** most of which exist as such in the plant. Others, however, result from fermentative action, in the presence of moisture, following injury or treatment of the plant tissues. For example, oil of wintergreen does not exist as such in the plant but results when the tissues are injured or bruised in some way, causing a reaction to take place between certain of the constituents to form the oil. Oil of tar, on the other hand, is a product of destructive distillation. These oils exist in separate oil glands, cells, or tubes in various tissues of the plant, such as rinds, leaves, fruits, roots, and barks. Few volatile oils are of a simple composition. They are, for the most part, mixtures of many chemical substances, some of which are solids in solution in the liquid portion. The solid portions of volatile oils are called **stearoptenes,** the liquid portions being **eleoptenes.** Camphor, menthol, and thymol are good examples of stearoptenes. They are obtained by chilling the respective oils to low temperatures and effecting a separation of the liquid portions.

Volatile oils are essentially hydrocarbons, chiefly terpenes associated with oxides, alcohols, phenols, aldehydes, ketones,

acids, and esters. A few of these oils contain nitrogen in the form of hydrocyanic acid, as in the case of **oil of bitter almond,** and sulfur in the form of a sulfide or a sulfocyanate, as in the case of **volatile oil of mustard.** The latter does not preexist in the plant but is produced by the interaction of glucosides and ferments and is obtained subsequently by distillation. While terpenes may comprise most of the volume of volatile oils, the odor, flavor, and medicinal properties of the oils are attributed to the nonterpene constituents. Terpeneless oils are those which have had their hydrocarbon constituents removed. Terpeneless oil of lemon is more expensive than the natural oil; but since it is a highly concentrated product, much less is required for flavoring purposes and it does not develop the undesirable terebinthinate odor that the natural product does upon standing.

Detailed descriptions, physical properties, and tests for identity and purity of the official volatile oils are to be found in the Pharmacopoeia and National Formulary. Certain properties of general interest will be mentioned here.

In most cases each volatile oil has a characteristic odor. Oil of turpentine, however, is free from odor when kept in an atmosphere of carbon dioxide; hence, its odor develops upon exposure to air. Most volatile oils are lighter than water although a few are heavier, oil of cloves being a good example of the latter. They are only slightly soluble in water, although there is considerable variability in this property.

All are sufficiently soluble in water to impart an odor to it. Pure volatile oils are said to be colorless, but most of them exhibit color ranging from pale yellow to dark brown. They are all soluble in alcohol and the other common organic solvents. They do not leave permanent stains on paper as do fixed oils, nor do they become rancid. Upon being exposed, some of them thicken, even to the consistency of resins. It should be borne in mind that certain of the volatile oils react violently with iodine. Their reaction with strong acids and strong bases varies with their composition and serves to identify them or aid in isolating certain important constituents.

It has been observed that the corks of certain of the bottles containing volatile oils become bleached. This is ascribed to the ozone produced by the oil. The proper storage of volatile

oils is important. The containers, preferably of amber glass, should be well filled, tightly stoppered, and stored in a cool, dark place.

The descriptions, physical properties, and tests for identity and purity in the Pharmacopoeia and the National Formulary are useful in identifying the oils and in detecting adulterations. Common adulterants are fixed oils, alcohol, cheaper grades of oil of the same kind, and, in some instances, paraffin. It should be borne in mind that the detection of adulterants in volatile oils is not an easy task.

Methods of Obtaining Volatile Oils

Inasmuch as volatile oils are of great importance to pharmacy, the ways in which they are obtained will now be reviewed.

The most frequently used method is that of steam distillation of the fresh or partly or completely dried drug. In the case of dried drugs such as cinnamon bark and cloves, enough water to cover them is added and they are allowed to macerate for a short period. Steam is then passed through them, the vapors carrying the oil over into the condenser. The oil separates as the distillate cools either on top of the water or, in the case of the heavier oils, at the bottom. The oily layers are then separated and purified. In the case of fresh herbs, such as peppermint, the crop is cut, and then packed into large stills. Steam is forced through the green material, and the oil is carried over with the distillate as already described. The operation calls for a steam-distillation outfit. It is not feasible to boil the mixture of drugs and water; therefore it is necessary to generate the steam in a boiler attached in the correct manner to the still.

Since oils, to some extent, are soluble in water, it is sometimes necessary to resort to the process of **cohobation,** which consists in returning the aqueous part of the distillate repeatedly to the still for redistillation. This minimizes the loss of oil.

Direct distillation without the aid of water is used to obtain certain of the volatile oils and oleoresins. Volatile oil of turpentine and copaiba are good examples of products obtained by this process. The residue left in the still after distilling off the oil of turpentine is rosin. Crude turpentine is described as a concrete oleoresin.

Destructive distillation is the process used to obtain the tar-like oils, such as Juniper Tar U.S.P. XII (oil of cade), which is not necessarily classed as a volatile oil.

The oils from the rinds of certain of the citrus fruits such as lemon, orange, and bergamot are obtained by **expression.** The oil is in the little oil pockets of the rind and may be released by pressure or, preferably, by scraping the rind to rupture the oil cells prior to expressing them or rubbing them against a sponge from which the oil may be expressed. The **ecuelle** method is that of rolling the round fruit in a bowl or trough, which is lined with innumerable spikes. The latter pierce the oil cells at the surface of the rind. The oil collects at the bottom of the apparatus.

The volatile contents of certain flowers and plants are so small that it is not possible to remove them by the means already indicated. In such cases the odorous principles of the plant are **macerated** with inodorous, bland oils or fats. The latter absorb the volatile principles which may be then removed in the manufacture of perfumes.

The method of **enfleurage** much resembles the process described in the preceding paragraph. In enfleurage, thin layers of inodorous fats are spread upon glass plates held in frames. Flowers are spread upon the glass and allowed to remain for several hours. A fresh charge of flowers may be used as often as is necessary, thoroughly to impregnate the fat. Fats that have been so impregnated may be used in pomades, or the odorous principle may be removed by alcohol. The method of enfleurage is not so important as it once was.

In recent years, low-boiling volatile solvents have been used to extract volatile floral principles by the percolation process. This is made use of by the perfume chemist. The volatile solvent may be removed by vacuum distillation. The residue is known as a **concrete.** The odorous principles of flowers that remain in the waxlike concrete may be removed by alcohol. Traces of any wax may be removed by chilling, the remaining product being called an **absolute.** These are costly products but have good odor value for the perfume industry.

The synthetic chemist is now able to manufacture many of the alcohol, aldehyde, ketone, and ester constituents of volatile oils,

thus removing the necessity for depending on the natural sources for oils and odorous principles. However, the synthetic products are not always to be preferred in the matter of delicacy of odor.

HYDROCARBONS

The term **hydrocarbons** pertains to a group of compounds composed of hydrogen and carbon. These exist as gases, liquids, and solids, but only the latter two classes are of use in pharmacy. Paraffin, petrolatum, and liquid petrolatum are common examples; they are referred to as mineral wax and mineral fats. Paraffin has waxlike physical properties and pharmaceutical uses but is chemically unlike beeswax and other waxes. Petrolatum and liquid petrolatum have many fatlike properties and uses but are nonsaponifiable and chemically very different from fats such as lard, tallow, olive oil, and a large group of oils and fats. These so-called "mineral" fats are stable and chemically neutral. When highly refined, they are quite tasteless, almost odorless, insoluble in water or alcohol, but soluble in ether, chloroform, carbon disulfide, petroleum, and fixed and volatile oils. The hydrocarbons are greasy to the touch and leave a permanent greasy stain upon fabrics. They do not become rancid and for this reason have found favor as ointment bases, although from the therapeutic standpoint their value has been questioned.

The gaseous members of this group include methane, ethane, propane, and butane. Natural gas, so important in the pharmaceutical laboratory, is composed chiefly of methane, ethane, and other hydrocarbons. It is obtained by drilling into gas pockets within the earth from which it is piped great distances to many parts of the country. Natural gas is odorless and very toxic. For these reasons odorous compounds are poured into the main pipe lines in order that escaping gas may be detected easily.

Source of Pharmaceutical Hydrocarbons

The hydrocarbons have their source in crude petroleum, which comes from the earth as a dark, greasy liquid with a characteristic, disagreeable odor. It has been called stone oil or rock oil and is used in liniments. In the process of refining, the gases are removed by distillation. After distillation the residue contains **liquid petrolatum, petrolatum,** and **paraffin.** These are

separated by distillation, or by chilling and expression, and then are subjected to further processes of purification.

Liquid petrolatum is known as **white mineral oil, paraffin oil,** or **liquid paraffin.** Two varieties are described, the **light** and the **heavy,** both being colorless oily liquids varying in specific gravity from 0.828 to 0.905.

Petrolatum is called **petroleum jelly** and is known in commerce as **cosmoline,** etc. It is usually yellowish to amber in color, with a characteristic fluorescent appearance, and is widely used as one of the constituents of ointment bases.

White petrolatum is referred to as **white petroleum jelly.** At one time it was obtained only from Russian petroleum, but it is now chiefly an American product, specially purified from petrolatum. This product has appeared in varying degrees of color, from a faint yellow to white. The pharmacist should select the brand most suited to his needs and order it by its trade name.

Paraffin is useful in pharmacy as a hardening agent in ointments. Some of its many valuable technical uses are the making of candles, wax paper, and floor polishes. Other products of a similar nature are **ceresin** and **ozokerite.**

Purified petroleum benzin is a volatile, highly inflammable official hydrocarbon. It is useful in pharmacy as a solvent for fats, resins, and similar bodies. It should not be confused with benzene, a product obtained by the destructive distillation of coal. In industry it is used in dry cleaning.

The student is referred to the Pharmacopoeia and the National Formulary for definitions, descriptions, physical properties, and tests for identity and purity for the official hydrocarbons.

ALCOHOLS

In using the term **alcohols** one usually thinks of **ethanol,** or **ethyl alcohol,** and also of **dehydrated alcohol** and **diluted alcohol,** all three of which are official. **Whisky** and **brandy** are also official and are nearly 50 per cent alcohol by volume, but are considered as representing a distinct class of alcoholic product.

Ethyl alcohol and dilutions of it are perhaps, next to water, the most widely used of all the solvents. Without it, processes and procedures in pharmacy would be greatly reduced. Alcohol is

miscible in all proportions with water, acetone, ether, chloroform, and petroleum benzin. It is a colorless liquid with a characteristic odor. Being volatile and inflammable, it can be used as a source of fuel and power. Alcohol is about 95 per cent ethanol and has marked preservative and antiseptic properties. Since it is a product of distillation, one would expect it to be produced in varying degrees of purity and to contain a great variety of impurities, depending on the care with which it is produced and rectified. Inasmuch as it is a constituent of a great variety of alcoholic beverages, there are many state and Federal regulations for handling it. These laws operate against the pharmacist in the exercise of his skill and knowledge as a manufacturer and a dispenser of drugs and medicines.

Ethanol (C_2H_5OH) is a hydroxy (OH) substitution product of ethane (C_2H_6), one of the hydrogens being substituted by a hydroxy radical. It may be so produced from ethane. However, yeast cells are able to produce it by acting upon saccharine solutions such as dextrose at a temperature of about 25 to 30°C. As the sugar undergoes fermentation, alcohol and carbon dioxide are produced as indicated by the following equation:

$$\underset{\text{dextrose}}{C_6H_{12}O_6} \rightarrow 2\underset{\text{alcohol}}{C_2H_5OH} + 2\underset{\text{carbon dioxide}}{CO_2}$$

In this process, when the concentration of the alcohol reaches about 14 per cent the yeast ceases to be active. The alcohol is then removed by distillation. By this means the alcohol is also concentrated and rectified.

In addition to alcohol and carbon dioxide, small quantities of other substances are produced in the fermentation process, including **fusel oil, glycerin, acids,** and **ether.** These give odor to the distillate and may be removed by redistilling the alcohol over chemicals such as quicklime and anhydrous sodium acetate. Alcohol may be dehydrated by adding freshly prepared quicklime or some other dehydrating agent to it and allowing the mixture to stand a few hours prior to removing the alcohol by distillation. Dehydrated alcohol has such an affinity for water that it must be carefully collected and stored in well-filled, tightly stoppered containers. For reagent purposes it is often necessary

to redistil alcohol over potassium hydroxide or lime in order to remove the acids, aldehydes, and other impurities.

Alcohol is official in the Pharmacopoeia, to which the student is referred for description and physical properties and tests for identity and purity. This applies also for diluted alcohol and dehydrated alcohol.

Alcohol of full strength is seldom used in preparing medicinals. Varying dilutions are used in the preparation of tinctures, fluidextracts, extracts, and solutions. When equal volumes of alcohol and water are mixed, there is a shrinkage in volume of about 3 to 5 per cent. This needs to be taken into account when definite volumes are specified. There is also a rise in temperature of several degrees in such a solution. It is well to permit the solution to cool to room temperature before using it in order to avoid errors in volume due to expansion and contraction with increase and decrease in temperature.

Proof spirit is a 50 per cent solution by volume of alcohol. A 100 proof alcohol solution would, in reality, be a 50 per cent alcoholic solution. Pharmacopoeial alcohol should be 189.8 proof or 89.8 deg. above proof. The United States government uses this method of determining the purity of alcohol or highly alcoholic solutions. In pharmacy, the amount of alcohol in solutions or preparations is stated in percentage by volume, although it may be reported in percentage by weight.

Congress passed a law in 1907 permitting the denaturing of alcohol. **Denatured alcohol** can be sold tax-free—hence, at a price much below that of tax-paid alcohol. A number of chemicals, such as alum, carbolic acid, formaldehyde, cresol, methyl alcohol, brucine sulfate, and diethylphthalate, have been used to denature alcohol. These usually render alcohol unfit for beverage purposes and for preparing medicinals, but not for technical uses. No permit is required for the purchase and use of completely denatured alcohol unless one expects to recover the alcohol. For recovery purposes special Federal permits are required.

Methanol, or **methyl alcohol** (CH_3OH), is commonly known as **wood alcohol;** other synonyms for it are **wood naphtha, methylic spirit, columbian spirit, colonial spirit,** and **pyroxilic spirit.** It is one of the products obtained from the dry distillation of wood

and is removed by distillation from the watery portion of this distillate following treatment with slaked lime. Further treatment of the rectified distillate with sulfuric acid removes the ammonia and other products. The methanol is then removed by distillation.

Methanol may be prepared also by causing water gas and steam to react by means of a catalyst. It is a colorless liquid having a peculiar, characteristic odor, a specific gravity of about 0.79, and a boiling point of about 66. It is usually about 99.5 per cent methanol, is a good solvent for fats, resins, etc., and is used extensively in industry. It is more expensive to manufacture than ethyl alcohol, is very toxic, and should not be used for making pharmaceutical preparations.

Glycerin is a polyhydric alcohol containing not less than 95 per cent $C_3H_5(OH)_3$. The glyceryl radical (C_3H_5) is found in all vegetable and animal fats and oils. The trihydric substitution product of this radical is glycerin, which is a clear, colorless liquid, sweet to the taste, with a slight odor, miscible in all proportions with alcohol and water, and immiscible in all the ordinary organic solvents and fixed and volatile oils. It has a specific gravity of about 1.25 and the consistency of a thick syrup and is pharmaceutically important as a solvent and a preservative. It is credited with preventing reduction of metallic salts in solution and being valuable as a solvent for preparations containing tannin.

Glycerin is nonpoisonous and has the property of absorbing moisture from the air. For this reason it should be stored in tightly closed containers. Being hygroscopic, it serves as a valuable constituent in certain extracts, pastes, and similar preparations to prevent drying and hardening. The glycerites of starch and tragacanth are good examples of the preservative and nondrying properties of glycerin. These properties make it valuable as an emollient for certain skin disorders. It also has some value as an antiseptic and is a constituent of many of the antiseptics, lotions, and gargles on the market.

Glycerin is obtained from fats and oils by the process of saponification as in the manufacture of soap and in the pharmaceutical laboratory in the manufacture of Lead Plaster N.F. VII. The latter is an insoluble hard soap and is washed in the process

to remove the glycerin and other soluble products. Glycerin was discovered in 1729 by Scheele, the Swedish apothecary, in the wash water from lead plaster. It was first produced commercially in this country about a century ago as a by-product of the lead-plaster industry. At about this time it came into use in pharmacy and medicine. When fats and oils are subjected to superheated steam under pressure, they are decomposed into fatty acids and glycerin. Glycerin can be prepared synthetically and also by fermenting beet-sugar molasses under proper conditions. The abundance of fats and oils in this country has made it unnecessary to resort to the two latter methods of production.

Crude glycerin is purified by distillation *in vacuo* or with steam. Coloring matter may be removed with charcoal and the distillation process repeated as often as is necessary to obtain the required purity.

Glycerin reacts with nitric acid to form **nitroglycerin,** which is an important explosive and is used in the manufacture of dynamite. Nitroglycerin has some value as a medicine, being official as a 1 per cent alcoholic solution known as Spirit of Nitroglycerin U.S.P. XII with a dose of 1 ♏. It appears also in tablets of nitroglycerin, dose $\frac{1}{100}$ g. Nitroglycerin products are dangerous drugs; and even the doses indicated may produce a violent headache. The student is referred to the Pharmacopoeia for descriptions, physical properties, and tests for purity and identity of these products.

ACIDS

An acid is a substance that, when acted upon, combined with, or neutralized with a base, forms a salt. In the presence of moisture or in solution, acids cause blue litmus paper to turn red. They also affect indicators such as phenolphthalein, methyl orange, and methyl red in solution. Aqueous solutions of acids contain hydrogen ions (H^+) and are sour to the taste.

Acids are commonly referred to as being (1) **inorganic,** such as **hydrochloric** and **sulfuric acids;** and (2) **organic,** such as **acetic** and **tartaric acids.** An example of further classification is furnished by the **halogen acids,** hydrochloric acid (HCl), hydrobromic acid (HBr), hydriodic acid (HI), and hydrofluoric acid (HF), which are derived from the four halogens, respectively.

These are sometimes referred to as the **hydracids,** those without oxygen. Another group of acids, containing oxygen, such as nitric (HNO_3) and sulfuric (H_2SO_4), are referred to as **nonmetallic oxygen acids.** A group of the organic acids, such as stearic, palmitic, and oleic acids, are termed the **higher fatty acids,** being derived from fats.

Acids exist as gases, liquids, and solids. One of the most common gaseous acids is hydrochloric acid, which is available as a solution, the gas, HCl, being readily soluble in water. The heavy acids such as nitric, phosphoric, and sulfuric are liquids. Of the well-known organic acids some are liquid, such as acetic and oleic. Others, such as citric, tartaric, tannic, benzoic, and salicylic, are solids, being white or very light in color and of crystalline structure. The heavy acids are soluble in water, as are the organic acids, citric, tartaric, and tannic. On the other hand, benzoic, salicylic, and the higher fatty acids are insoluble.

Aqueous solutions of the acids are sour to the taste. Inorganic acids, such as hydrochloric, nitric, and sulfuric, are corrosive to the tissues and destructive to fabrics, wood, and paper and to most apparatus in the laboratory except glassware. Strong acids need to be handled with extreme care; careless handling has resulted in much damage to property and in serious accidents.

The organic acids, as such, perhaps find their way into medicines more often than do the inorganic acids. Citric and tartaric acids are necessary constituents of granular effervescent salts, a popular kind of medicament.

It is not possible to deal with the subject of acids in detail at this time. For a more complete discussion of the acids official in the Pharmacopoeia and the National Formulary the student is referred to these texts.

ALKALOIDS

Alkaloids are an important class of plant bases of complex chemical structure. A few are of animal origin. They all contain nitrogen as well as carbon and, with a few exceptions, oxygen. The term *alkaloid* means alkali-like. Most of the alkaloids react with acids to form salts, which are more soluble and for this reason are the most generally used in medicines.

Most of the alkaloids are solid, although a few exist in the liquid form. **Nicotine,** one of the most potent of the alkaloids, is a liquid. Alkaloids are said to exist in nature in the form of salts such as malates, tannates, and citrates. In opium, the alkaloids are combined with meconic acid; in cinchona, with quinic acid. In 1817, Sertürner described morphine as a new salt-forming substance. His discovery was followed immediately by reports from other workers and opened the way for a series of discoveries of alkaloids and other plant principles. The alkaloids were attractive to early pharmaceutical chemists because they possessed marked physiological action, many being very potent. As a rule they are bitter to the taste, insoluble in water, but soluble in the usual organic solvents. They are mainly crystallizable, although some are amorphous and a few are liquid, and are usually colorless, although **berberine** is yellow. Most of them show optical activity and have a definite melting point.

The occurrence of alkaloids is restricted to a comparatively few plant families. Occasionally the same alkaloid is found in more than one family. In a few instances, plants yield more than one alkaloid. Nux vomica contains two alkaloids, opium twenty-one, and cinchona thirty-two. It is unusual for a plant to yield more than four alkaloids. They may be found in any or all parts of the plant, such as the stem, bark, root, seed, and leaves. Many explanations have been offered for the presence of alkaloids in plants, but none is wholly satisfactory. In recent years, a number of alkaloids have been synthesized; this includes procaine and many other local anesthetics that are acceptable substitutes for cocaine although chemically unlike it.

The names of the alkaloids end in **-ine** in English and *-ina* in Latin. For example, morphine in English is *morphina* in Latin. This system of nomenclature is generally used, notably in the Pharmacopoeia and the National Formulary.

The medicinal value of many drugs and their preparations is dependent on their alkaloid content. A number of reagents have been developed for testing for the presence of the alkaloids. Among the most common are Mayer's reagent, Wagner's reagent, and solutions of tannic acid, picric acid, and mercuric chloride. The alkaloids are sensitive to these reagents and are detected in

small amounts by the formation of marked precipitates when the reagents are added to their solutions.

Alkaloidal assay is a subject of study and interest to the pharmacist and the pharmaceutical chemist. The details of these assays cannot be given here except to say that some of the alkaloids may be assayed chemically, while others must be assayed biologically.

A number of the natural alkaloids and their salts and also salts of several synthetic alkaloidal derivatives are official in the Pharmacopoeia and the National Formulary. These include atropine, codeine, caffeine, ephedrine, morphine, quinine, and strychnine and their salts. The reader is referred to these texts for descriptions, tests for identity and purity, and the preparations in which the official alkaloids appear. It will be observed that strychnine and its salts have a wide use in a variety of medicinals. Perhaps the most important of the medicinals in common use are the alkaloids of opium, especially morphine and codeine. Science has been unable to produce acceptable synthetic substitutes for these valuable drugs, although much attention has been given to the problem.

GLYCOSIDES

The glycosides, often referred to as **glucosides,** constitute a large group of plant principles. They are complex bodies described as ester- or etherlike compounds of carbohydrates. When subjected to the action of dilute acids or ferments, they yield glucose, or some other hexose, or perhaps a pentose, in addition to other substances. The latter are likely to be complex benzene compounds. The term **glycoside** is now used as a general name for the group, irrespective of the sugar present, and is perhaps a better term than glucoside.

The complexity of glycosides may be illustrated by **digitonin** and its decomposition products, as follows:

$$\underset{\text{digitonin}}{C_{55}H_{90}O_{29}} + 5HOH = \underset{\text{digitogenin}}{C_{26}H_{42}O_5} + \underset{\text{galactose}}{4C_6H_{12}O_6} + \underset{\text{xylose}}{C_5H_{10}O_5}$$

(digitonin + water = digitogenin + galactose + xylose)

With a few exceptions the glycosides do not contain nitrogen. **Amygdalin,** for example, yields dextrose, benzaldehyde, and hydrocyanic acid when hydrolyzed. The enzyme **emulsin** in

contact with amygdalin in the presence of moisture effects this hydrolysis. With each glycoside it is assumed that there is associated a distinctive enzyme which possesses the power of hydrolyzing it. Such enzymes possess the power of hydrolyzing several glycosides. The hydrolysis of glycosides may also be accomplished by boiling them with dilute acids or alkali solutions. It happens that the hydrolysis product of glycosides is of greater pharmaceutical importance than the glycoside itself. The benzaldehyde just mentioned and volatile oil of mustard are good examples. The latter is chiefly **allyl isothiocyanate,** a poisonous product, and is produced naturally by the action of the enzyme **myrosin** on the glycoside **sinigrin;** these substances are present in the mustard seed. Hydrolysis takes place in the presence of moisture, which may have to be added, and warmth. The volatile oil of mustard does not **preexist** in the seed but is formed under the conditions indicated and may be removed by steam distillation. The two products of glycosidal hydrolysis, benzaldehyde and volatile oil of mustard, are prepared synthetically, as are also salicin, methyl arbutin, and others. A few glycosides that have been synthesized are not known in nature.

Although glycosides are important plant products, very few are official. They do not always constitute the active constituents of plants. When their action is important, they are likely to be used in their natural combination rather than alone as purified products. There are, of course, exceptions to this general rule.

They have the ending **-in** in English. Those which are official have the **-in** Latinized to *-inum,* as illustrated by salic*in*, *salicinum.*

It should be borne in mind that glycosides are characterized not by the glucose but by the nonglucose part of the compound. The nonglucose products of glycosides are called **aglucons** and possess widely varying medicinal properties. This has led to a general classification according to action, such as astringent, purgative, bitter, sweet, and heart glycosides.

No general tests for the identity and purity of glycosides are applicable. A quantitative determination of the reducing sugars, before and after hydrolysis, may be made. The nonglucose cleavage product is, in some instances, easily detected. Certain

of the heart glycosides are assayed biologically. The real purpose and significance of glycosides in the economy of the plant is largely a matter of opinion. Perhaps they protect the plant by acting as antiseptics.

SAPONINS

The saponins are termed the **frothing glucosides.** They are closely related to the glycosides but differ from them in their chemical constitution and physiological action. They are usually amorphous, although a few are crystalline, and bitter to the taste. Finely powdered drugs containing them are irritating to the mucous membrane and are sometimes classed as sternutatories. With a few exceptions saponins are toxic, especially to cold-blooded animals, bringing about the destruction of the red blood corpuscles. Some saponins are effective poisons for fish and form poisonous compounds with cholesterol. When mixed with grains fed to domestic animals, certain plant seeds that contain saponins cause loss of life.

Because of their poisonous properties, saponins have a limited use. Those which are less toxic have been used as emulsifying agents, behaving like solutions of soap even in dilutions up to 1 in 10,000. Tincture of soap bark has been used as an emulsifier for external products. Saponins of this kind find use as detergents for cleaning certain fine fabrics, in disinfectants to increase the miscibility of the latter with water, and in foaming fire extinguishers. It has been said that the foam in root beer, beer, and ale is due to the presence of harmless saponins in the extracts used to prepare the syrup from which the beverage is made.

Saponins, for the most part, are soluble in water and are hydrolyzed in a manner similar to that of the glycosides when heated with dilute mineral acids. Several are crystalline, although most are colloidal and dialyze with difficulty. They are insoluble in ether, benzene, chloroform, and cold alcohol but are soluble in hot alcohol.

From a chemical viewpoint, they may be classed as neutral or acid saponins. Upon hydrolysis they yield a variety of sugars. Being water-soluble, saponins are obtained from the roots, leaves, seeds, etc., as aqueous extracts, from which they are precipitated.

Sarsaparilla U.S.P. XII yields a mixture of glycosides, among which are **parillin** and **sarsaponin.** Quillaja N.F. VII yields **sapotoxin** and **quillaic acid,** which are toxic and nontoxic, respectively. *Saponaria officinalis* L. yields about 5 per cent, *Polygala senega* L. about 2.5 per cent, and *Agrostemma githago* L. about 6 per cent of sapotoxin. The latter plant is corn cockle, which grows as a weed in wheat crops and the seeds of which get mixed with the grain, causing loss of life when fed to animals because of the poisonous sapotoxin present. The common horse chestnut is a good source of saponins. Yucca rhizomes are reported to contain as much as 20 per cent saponin. The results of recent investigations indicate that the cardiac glycosides and the saponins are related to the sterol glycosides.

ENZYMES

Enzymes are often referred to as **ferments.** They are active substances, behave as catalysts, and are known chiefly by the results they produce. They are complex bodies having many of the properties of proteins; their colloidal nature makes the separation of pure enzymes almost impossible although they are adsorbed upon such substances as kaolin and infusorial earth. They are found in both animal and vegetable tissue and are regarded as the catalytic agents of the living cells. They are produced by the living cell but are independent of the cell in their action. They are not living bodies because they are unable to grow or reproduce themselves.

Enzyme activity, so far as is known, is confined almost wholly to reactions with organic compounds. **Digestion** is a term used to designate the decomposition of organic substances by certain organic juices. If a foul odor results, the process is termed **putrefaction.** The term **fermentation** has been applied to the process of digestion that results in the liberation of gas. Varieties of fermentation are termed (1) spirituous, (2) acid, and (3) putrefactive. The process of fermentation was at one time ascribed to the presence of a **ferment,** an early term used to describe substances that are now called enzymes.

Pasteur proved that grape sugar produces alcohol and carbon dioxide (CO_2) as a result of the life activities of yeast cells. He defined fermentation as "life without oxygen." Reactions by

ferments have been referred to as those occurring in contact with the living cell, and enzymatic reactions as those reacting separately and apart from the cell. Such differentiation between ferment and enzyme is no longer tenable.

Inorganic catalysts are definite chemical substances, but the chemical structure of enzymes is not known. Inorganic catalysts are usually capable of catalyzing many reactions. Enzymes are much more specific, some of them being absolutely specific in their action. The proteolytic enzymes do not attack fats, and the lipases do not split proteins.

Many of the important physiological processes essential to life, in both animals and plants, are dependent on the action of enzymes. They play an important role in the production of many industrial items such as alcohol, acetic acid, and many other products.

The earliest of the enzymes to be named was **pepsin.** It was established more than one hundred years ago that some specific substance is responsible for gastric digestion. Somewhat later, the existence of **trypsin** in the intestine was also confirmed. Other enzymes were later discovered by means of their characteristic reactions. The actual existence of enzymes is hard to establish, but the mechanism and nature of their reactions have interested both chemists and physiologists during recent decades. As a result, many of the anomalies attributed to enzyme reactions have been explained.

Enzymes, as a rule, are sensitive to light and heat. It has been stated that none will survive a temperature of 100°C. and that many are affected by temperatures of about 50°C. It is well known, however, that increased temperatures create conditions favorable to the activity of enzymes and low temperatures retard their action. The enzymatic substances that are commonly known are colloidal in character, making the separation as pure enzymes almost impossible. Each enzyme has a pH range at which it functions most efficiently and the rates at which many of them react vary with the acidity of the solution. However, certain enzymes act best in a neutral, or alkaline, medium.

The protein nature of enzymes is attributed to the presence of protein impurities. Hence, as one part of **rennin** is able to coagulate over 100,0000 parts of casein, the action is apparently not

one of molecular proportions and may be regarded as being a catalytic action. Antiseptics are capable of retarding or destroying the action of enzymes. In the fermentation of dextrose by yeast, in which alcohol and carbon dioxide are products, the reaction stops when the alcoholic content of the reaction mixture reaches 14 to 16 per cent. Enzymatic action may be inhibited or accelerated by certain organic compounds and inorganic salts. For example, the presence of tannin in certain vegetable extracts renders the enzymes inactive. Dried enzyme products are reasonably stable, but those which are not dried need to be preserved.

The following classification of enzymes is a modification of that given by Greisheimer.[1]

1. **Amylases,** such as **ptyalin** found in saliva and **amylopsin** in pancreatic juice; both hydrolyze starch to maltose.

2. **Disaccharases. Sucrase** in the intestinal juice hydrolyzes sucrose to glucose and levulose. **Lactase** in the intestinal juice hydrolyzes lactose to glucose and galactose. **Maltase** in saliva, pancreatic juice, and intestinal juice hydrolyzes maltose to glucose.

3. **Lipases.** Gastric lipase, found in the gastric juice, hydrolyzes fats into glycerol and fatty acids. Pancreatic lipase, known as **steapsin,** is found in the pancreatic juice and also hydrolyzes fats into glycerol and fatty acids.

4. **Proteases.** Gastric protease is found in the gastric juice. These proteases are commonly known as **pepsin** and, in the presence of hydrochloric acid, hydrolyze proteins into proteoses and peptones. Pancreatic protease, known as **trypsin,** is found in the pancreatic juices and hydrolyzes those proteins which escaped the gastric digestion. The intestinal protease, known as **erepsin,** is found in the intestinal juices and hydrolyzes peptones and peptides to amino acids.

Details of the physiology involved in these digestive processes are given in the reference cited[1] and may be found in other good texts on physiology.

Much has been written in recent years on the subject of enzymes. One cannot read the literature without being

[1] E. M. GREISHEIMER. "Physiology and Anatomy," J. B. Lippincott Company, Philadelphia, 4th ed., 1940.

impressed with the importance of these bodies. They are absolutely essential to life in both plants and animals. They are essential also to the success of many industrial processes and laboratory procedures, in diagnosis, and in the treatment of disease.

STUDY QUESTIONS

1. Nineteen groups of natural plant products have been described in this chapter. If you grouped those most closely related together, how many classes would you have?

2. Distinguish gums from mucilages.

3. Why is copaiba called a balsam when it is an oleoresin?

4. Why is crude cotton nonabsorbent, and how is it treated to make it absorbent?

5. If the plant manufactures starch in the leaves, by what mechanism is it stored in the roots and seeds?

6. Name the general classes of sugar, and give an example of each class.

7. How do sucrose and lactose differ in respect to solubility and sweetness?

8. Compare gum resin, oleoresins, resins, and balsams, and give distinguishing features of each.

9. How important are fats to the soap industry? Explain your answer.

10. Name several waxes, and give their pharmaceutical uses.

11. Give the physical characteristics of volatile oils, and state how they are obtained.

12. Name several hydrocarbons, and give their physical properties.

13. What is denatured alcohol?

14. Define an acid, and give the general classes.

15. Give the properties of alkaloids, and name several.

16. Discuss the properties of glucosides and saponins, and give examples of each.

17. Describe the character and importance of enzymes, and name those commonly known.

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APPENDIX I

A SUGGESTED LIST OF BOOKS FOR THE PHARMACIST'S LIBRARY[1]

General

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BENNETT, H. "Chemical Formulary," Chemical Formulary Co., 950 Third Ave., New York, Vol. 1, 1933; Vol. 2, 1935; Vol. 3, 1936; Vol. 4, 1939; Vol. 6, 1943.

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BRISCOE, HERMAN T. "General Chemistry for Colleges," Houghton Mifflin Company, Boston, 2d imp., 1938.

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[1] The reader is referred to lists published in *The American Druggist* No. 4 (October, 1939) 42–43, 136; No. 5 (November, 1939) 48, 109; No. 6 (December, 1939); No. 1 (January, 1940) 66, 68; "Remington's Practice of Pharmacy," pp. 1859–1860; also to reviews in the *Journal of the American Pharmaceutical Association*, The *American Journal of Pharmaceutical Education*, *American Professional Pharmacist*, and *Drug and Cosmetic Industry*.

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SOLLMANN, TORALD H. "A Manual of Pharmacology," W. B. Saunders Company, Philadelphia, 6th ed., 1942.

"The Merck Manual," Merck & Co., Inc., Rahway, N.J., 7th ed., 1940.

"The Pharmacopoeia and the Physician," American Medical Association, 535 North Dearborn St., Chicago, 1st series, 1937. The second series is in the process of publication and may be purchased in reprint form from the Chairman of the Committee of Revision of the Pharmacopoeia of the United States of America, Philadelphia.

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AUTENREITH, WILHELM. "Laboratory Manual for the Detection of Poisons and Powerful Drugs," translated by Wm. H. Warren, The Blakiston Company, Philadelphia, 6th American ed., 1928.

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SCOVILLE, WILBUR L., JUSTIN L. POWERS, and G. E. CROSSEN. "The Art of Compounding," The Blakiston Company, Philadelphia, 7th ed., 1943.

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COMSTOCK, JOHN HENRY, ANNA BOTSFORD COMSTOCK, and GLENN W. HERRICK. "A Manual for the Study of Insects," Comstock Publishing Company, Inc., Ithaca, N.Y., 22d ed. rev., 1938.

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APPENDIX II

MINIMUM STANDARD EQUIPMENT FOR A PHARMACY[1]

Balance, dispensing torsion, capacity 500 Gm., sensitivity 15 mg.
Balance, prescription, capacity 120 Gm. each pan; sensitivity 2 mg.
Bath, water, copper, 6 in.
Beakers, lipped, pyrex, assorted sizes, 50 to 2,000 cc.
Bottle capper (1)
Bottle caps for magnesia citrate bottles
Bottle, graduated, 1,000 cc.
Bottles with droppers, amber or other color, assorted sizes
Bottles, magnesia citrate, 200 cc. and 350 cc.
Bottles, prescription, ungraduated, (without metal caps) assorted sizes
Bottles, reagent, glass-stoppered, narrow-mouthed, amber, assorted sizes
Bottles, reagent, glass-stoppered, narrow-mouthed, assorted sizes
Bottles, reagent, wide-mouthed, bakelite caps, assorted sizes
Bottles, wash, one or more
Boxes, suppository, assorted sizes
Burettes, 50 cc. (2)
Burners, bunsen (2)
Capsule machine (1)
Casseroles, porcelain, assorted sizes
Cork borers (1 set)
Corks, assorted sizes and tapers
Cotton, purified
Counter balance, capacity 7 lb., sensitivity 20 gr.
Double boiler, suitable size (1)
Electric hot plate, three heat (1)
Evaporating dishes, porcelain, assorted sizes
Filter paper, hard, qualitative, assorted sizes
Flasks, Erlenmeyer, pyrex, assorted sizes
Flasks, volumetric, glass-stoppered (three sizes)
Funnels, long stem, 60-deg. angle, 3 in.
Funnels, plain, 3, 4, and 6 in.
Funnels, straining, hard rubber, assorted sizes
Gauze (cheesecloth)
Graduates, conical, duplex scale, 1 f℥ (5 cc.) to 32 f℥ (1,000 cc.)
Graduates, cylindrical, 10, 25, 50, or 100 cc.
Graduates, cylindrical, glass-stoppered 250 and 500 cc.
Homogenizer, hand (1)
Litmus paper, blue and red

[1] For a detailed study of equipment requirements, the reader should also refer to a tabulation in *Drug Topics* **54** (No. 23), 31 (1938); and **54** (No. 25), 19, 22 (1938); to "The Professional Pharmacist," The American Pharmaceutical Association, 1938, pp. 5–6; to "Basic Material for a Pharmaceutical Curriculum," McGraw-Hill Book Company, Inc., New York, 1927, pp. 322–330; to the *Journal of the American Pharmaceutical Association Practical Pharmacy Edition* 1, 9–12 (1940).

Mortars and pestles, glass, assorted sizes
Mortars and pestles, wedgwood, assorted sizes
Muslin
Ointment pots with bakelite or suitable durable caps, assorted sizes
Percolator packer and suitable weights
Percolators, conical, glass, assorted sizes to 1 qt. size
Percolators, cylindrical, glass, assorted sizes to 1 qt. size
Pipettes, measuring, volumetric, 10 cc. graduated to 0.1 cc.; 1 cc. graduated to 0.1 cc.; 1 cc. graduated to 0.01 cc.
Pipettes, transfer, assorted sizes
Prescription files
Rack, test tube (1)
Ring stand (retort), iron, complete with rings
Rubber stoppers, one- and two-holed, assorted sizes
Rubber stoppers, solid, assorted sizes
Sieves, brass, standard, complete set
Silk, bolting
Spatulas, rubber, assorted sizes
Spatulas, stainless steel, assorted sizes
Spatulas, stainless steel, pill
Stirrer, electric (1)
Stirring rods, glass, assorted lengths and diameters
Stirring rods or spoons, assorted sizes
Suppository machine and molds (1)
Test tubes, pyrex
Thermometers, to 360° graduated to 0.1°
Tubing, glass, assorted diameters
Tubing, rubbers, red, assorted diameters
Watch glasses, 3, 4, and 6 in. in diameter
Weights, avoirdupois, ½ oz. to 7 lb.
Weights, metric, brass, nickel plated, 1 mg. to 100 Gm.
Weights, metric, brass, nickel plated, 1 Gm. to 500 Gm.
Weights, metric, 10 Gm. to 10 Kg.
Weights, apothecaries', brass, 1 gr. up (not coin weights)
Wire gauze, asbestos center, 5 by 5 in.

Additional equipment may be needed for special types of work. If the pharmacist is specializing in the preparation of parenteral solutions or is conducting analytical work of various kinds, specialized equipment will be necessary.

The equipment listed above may be purchased from a number of reliable laboratory supply houses. The pharmacist should have the catalogues of several such houses. If equipment is being purchased in quantity, lists should be submitted to these concerns for quotations.

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