AN INTRODUCTION TO MEDICAL MYCOLOGY

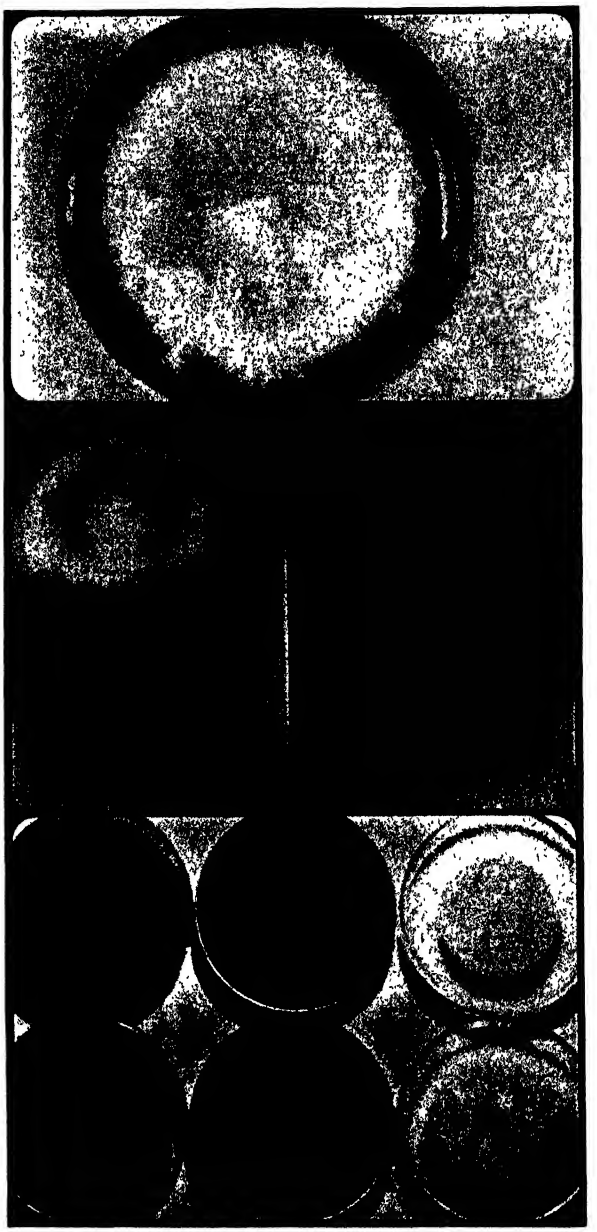

PLATE I. Development of pigment at the base of a fungus colony growing on an artificial medium. The yellow hue is characteristic of Microsporum lanosum, while the port-wine color is characteristic of Trichophyton purpureum. In the lower group, pigment developed only in mediums containing one of certain monosaccharides and was not synthesized when the available sugar was a disaccharide. (See p. 10.)

AN INTRODUCTION TO MEDICAL MYCOLOGY

by

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Preface to the Third Edition

IN THE nine years since the first edition of this book was presented (with some temerity), there has been a considerable advance in the knowledge of fungous disease. Many more workers are now engaged in either part-time or full-time research in this branch of medicine. The knowledge of fungous disease has been more generally disseminated and physicians, particularly dermatologists, have become proficient in the laboratory diagnosis of the various fungous diseases. It is heartening to see that clinical mycology has awakened such an interest among physicians. A glance through the program of almost any regional or national dermatologic meeting will disclose one or more papers of merit on topics related to the mycoses. There are fewer and fewer reports of cases without careful laboratory confirmation. This would indicate that mycology is an important and practical subject. It is hoped that in the revision of the text for this third edition, the many advances which have occurred since 1943 have been sufficiently abstracted without adding too greatly to the length of the book. The main purpose of the book, as its title implies, is to serve as a primer. It does not pretend to include all the many controversial details and involved technical aspects of the subject.

The general plan of the book has been retained. The contents are divided into two parts. The first deals with the clinical, theoretical and experimental aspects of the subject; the second outlines the laboratory procedures useful in examining a patient suspected of having one of the various mycoses. The characteristics and habits of the habitual fungous parasites are described. An attempt is made to emphasize important phases of mycology, the common diseases receiving more attention than the rare ones. Since the pathogenic flora varies in different parts of the world, our emphasis on certain fungi as important in New York may not apply to the same degree in other localities. The bibliography is not a complete compilation. It contains articles which we think are important for their originality and their value in teach-

ing. The majority of the references concern articles available in English.

It may be reiterated that pathogenic fungi are rarely found on the normal skin. Thus, when such micro-organisms are present, the finding is of etiologic importance in confirming a diagnosis of fungous disease. It is further notable that pathogenic fungi do not multiply or thrive in the presence of acute inflammation. For that reason the finding of pathogenic fungi in eczematous tissue is of prime significance. It is unlikely that fungous disease would supervene on contact dermatitis.

It is a pleasure to repeat words of gratitude to our former teachers, Drs. Fred D. Weidman and J. Gardner Hopkins, for awakening our interest in the problems of medical mycology. During the years preceding the first edition our laboratory was situated in the dermatologic department of the New York Post-Graduate Medical School and Hospital and later in the Skin and Cancer Unit of that institution. Dr. George M. MacKee was our Chief and he provided us with facilities for many of our investigations. In the fall of 1939, we transferred our laboratory to New York Hospital where we have since been. Dr. Eugene F. Du Bois and, later, Dr. David P. Barr encouraged us to continue our work and have given us a splendid opportunity under almost ideal surroundings. For seven years our projects were supported financially by the John and Mary R. Markle Foundation.

It affords us pleasure to acknowledge the help we have received from colleagues in many parts of the country both by constructive criticism of former editions and by the submission of supporting material. Dr. Harold L. Temple kindly provided and interpreted several radiographs, Dr. Clement B. Potelunas read the proof and Miss Eleanora Beemer generously provided the requisite secretarial assistance. The Year Book Publishers have been patient with demanding authors. The technical work in the book is all that could be desired.

We hope that this edition will be received with no less indulgence than those which preceded it.

—George M. Lewis
—Mary E. Hopper

June, 1948.

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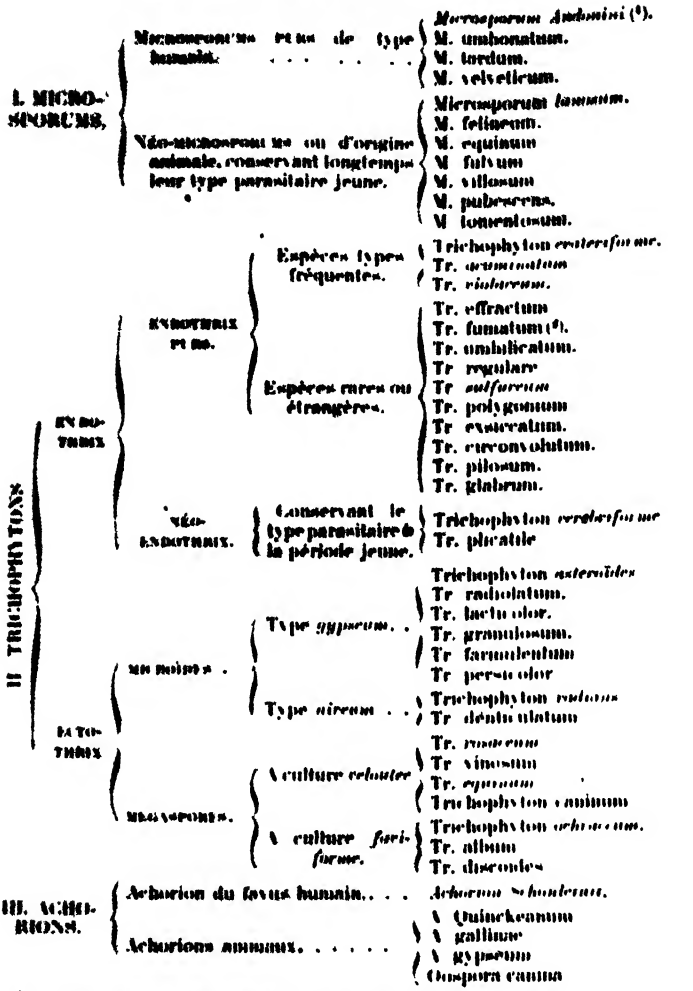
PART ONE

CLINICAL, THEORETICAL AND EXPERIMENTAL ASPECTS



(1) Les espèces les plus importantes ont leur nom en italique.

(2) A côté du *Trichophyton fumatum*, et, en tout cas, parmi les Trichophytons endothrix, il faudra bientôt faire place à deux nouvelles espèces, isolées à Vienne, dans le service de M. le Prof. Finger, par le Dr Mingazzini, l'une : *Trichophyton faciale* à culture cérébriforme, poudreuse et craquelée, présente en son centre une bourgeonnure blanchâtre, différente, caractéristique sur milieu d'épreuve. L'autre : *Trichophyton aquigenes*, présente une bourgeonnure centrale analogue mais de couleur bistre, neutre, non poudreuse et semblable à une éponge brune déposée sur une arène poudreuse, craquelée.

FIG. 1. Sabouraud's classification of the ringworm fungi. (*Reproduced from Les Teignes, Paris, Masson & Cie, 1910.*)

CHAPTER I

Historical Review

THE name of Sabouraud is prominent in any discussion on the development of the science of mycology. With the publishing of his book, *Les Teignes,* in 1910, the subject was demonstrated to be on a sound and practical basis. The interest engendered by this well written and beautifully illustrated book has continued to the present time. Sabouraud's researches brought mycology back to the attention of physicians when it had been almost forgotten.

This science is usually said to have begun as far back as 1677, when Hooke, using a magnifying lens, found that yellow spots on roses consisted of living threadlike organisms. In 1839 Langenbech described the fungus causing thrush and Schoenlein the cause of favus. Gruby described the cause of tinea circinata in 1842, and four years later Eichstedt found a fungus in scales of tinea versicolor. Tilbury Fox described tinea pedis in 1870. The brilliant researches of Pasteur and his contemporaries had temporarily caused mycology to be forgotten; as previously mentioned, it remained for Sabouraud to focus attention on the scientific aspects of a neglected subject.

Since the publication of Sabouraud's book, the workers have been legion; their progress cannot be concisely treated here with any justice to them or to the related subjects. We shall attempt to bring out the sequence of important advances under the respective headings. It would, however, be unfair not to mention Whitfield who first determined the pathogenic role of Epidermophyton inguinale in tinea pedis and whose formula is known to physicians in all parts of the world, Castellani for his work on the tropical mycoses, Jadassohn and Bloch for their researches, particularly in the immunology of fungous diseases, Miescher, Bruhns and Alexander for their work on the dermatophytes and de Beurmann for his inquiry into sporotrichosis.

Much of the best work in medical mycology has been undertaken in this

country. The names of Weidman, Hopkins, Benham, Jacobson, Dodge, Moore, Mitchell, Henrici, Emmons, Williams, Davis, Martin, Shaw and Conant come to mind, but these investigators are only a few of the clinicians, teachers and research workers in the United States who are actively engaged in furthering knowledge of this specialized field. It is of interest to note that nearly all the American medical mycologists are, coincidentally, either dermatologists or actively associated with dermatologic departments. That this is no chance association is attested to by the fact that, almost invariably, skin manifestations of the mycoses appear at some stage of their invasion of the body. Dermatologists are thus better versed in mycologic diseases than any other group of physicians.

Delineation of disease syndromes, evaluation of new species of pathogenic fungi, inquiry into improved methods of diagnosis, research into abstract biologic and biochemical problems and attempts to improve therapy have constituted some of the lines of endeavor. During World War II, interest in fungous diseases increased as members of the armed forces were stationed in all parts of the world. So far as the common fungous diseases encountered were concerned, no variation from the findings in civilian life was noted. However, on the basis of possibility of spread, some uncommon diseases of limited distribution, such as paracoccidioides, mycetoma and tinea imbricata, received considerable attention. To date no reports have shown any spread of these or of other unusual fungous diseases in this country. It is apparent that in medical mycology much important work remains to be done.

CHAPTER II

Classification of Fungi

FUNGI are microscopic members of the plant kingdom. They are included in the phylum of Thallophyta, in which there is no differentiation into roots, stem and leaves. There is further division into the orders of Algae and Fungaceae. Since the latter do not contain chlorophyll, they are unable to carry on photosynthesis. Fungaceae are divided into Bacteria, true fungi and Myxomycetes. The true fungi are divided into four subclasses; the most important subclass consists of Hyphomycetes, or fungi imperfecti, which include practically all the fungi pathogenic to human beings.

There have been many attempts further to classify and arrange the fungi which cause ringworm. Most of those who have studied the subject are dissatisfied with the existing subdivisions but realize that a botanic solution of the problem is at present impossible. It is usual to classify the fungi imperfecti which cause ringworm as dermatophytes. Sabouraud pointed the way to a purely clinical approach, and his classification of the superficial dermatophytes has been widely used. We believe that a modification of Sabouraud's arrangement (to suit the flora in this country) is sufficient for all who are not essentially botanists.

In Sabouraud's classification, fungi having small spores in which the elements are found in mosaic arrangement and in profusion on the surface of the hair are known as Microspora. The next group comprises Trichophyta, divided into endothrix, which invades the hair shaft with the formation of large spores in linear arrangement, and ectothrix, which forms chains of spores external to the hair. The endothrix micro-organisms are usually not inoculable into laboratory animals, whereas the ectothrix fungi are often pathogenic for them. The genus Achorion includes only one common pathogen, the cause of favus. It may be well to drop this term and include Achorion with the endothrix Trichophyta. The term "Epidermophyton" denotes lack of invasion of a hair follicle.

CHAPTER III

Structure of Fungi

STRUCTURALLY, fungi consist of vegetative elements and of fructification, or spore, forms. With few exceptions, in which the vegetative form consists solely of budding cells, the pathogenic fungi all form hyphae. These vegetative, filamentous structures are irregularly segmented and show some variation in form, according to the species. This is the form in which fungi are chiefly present in the human body. The structures connected with fructification are more specific, forming the basis for the identification of species. They are rarely present except in artificial cultures. Only asexual forms can be demonstrated. Fungi imperfecti are considered to be degenerated from other forms, which have perfect stages of development, and in some instances the relationship can be surmised. The subject is further considered in Part Two of this book, with the individual species of fungi.

CHAPTER IV

Physiology of Fungi: Requirements for Growth and Reproduction

WHEN conditions are optimal, the vegetative portion of a fungus increases and develops. If conditions are adverse, the fungus has a tendency to produce spore forms, which are more resistant. The following brief discussion presents some of the known extrinsic factors requisite for the full development of fungi.

The fungi classed as dermatophytes (which are responsible for the superficial infections) are usually found in relation to keratin, occurring in the stratum corneum, in the substance of nails, in or on hairs or in the hair follicles. This dermatropism has been subjected to scrutiny by a number of investigators. The inability of these fungi to live or reproduce in the internal organs and tissues is remarkable. Other fungi are able to invade the deeper portions of the tissues and seldom, if ever, are found in superficial locations.

1. TEMPERATURE

Most pathogenic fungi grow well at room temperature and more vigorously at body temperature. In the summer, fungi in culture develop more rapidly and the character of the growth is different from that of the same strain during the winter months. The counterpart in the clinical features of fungous infections is well known.

2. MOISTURE

One of the factors thought to be important in predisposing toward fungous infection of the toes is the moisture normally present or due to lack of drying after a bath or other conditions. It is well known that in culture, growth at low humidities is slow. The water requirements of

fungi, however, vary considerably according to the species. The normal habitat of some of the lower fungi is in the depth of a body of water. Others grow well on the surface of a liquid medium. Most pathogenic species of fungi grow best on a semisolid or solid stratum. Fungi may remain dormant for some time under natural or artificial conditions of drying, being capable of revival with the addition of moisture.

3. OXYGEN

With the exception of Actinomyces bovis, the common pathogenic fungi require oxygen for life and development. Lacking sufficient oxygen, reproductive bodies are sparse; they may be stimulated to develop by an excess amount of oxygen.

4. LIGHT

In some mycoses, such as tinea versicolor, the eruption is almost invariably confined to a covered portion of the body. The fungicidal action of certain light rays has been considered as a possible explanation. In our experience the growth of fungi has been almost equal in absolute darkness, subdued light and bright light. Certain ultraviolet rays have an inhibiting but not lethal effect. In our hands roentgen rays and radium have had little action as lethal agents, although some observers have reported inhibitory action on certain fungi.

5. NITROGEN REQUIREMENTS

The manner in which the dermatophytes utilize the amino acids in keratin has been the subject of considerable speculation and some careful research. A characteristic of all keratin is its chemical stability. According to Nickerson and Williams, no enzyme has yet been found that actually hydrolyzes a keratin. They believe it is possible that the dermatophytes act on keratin not through primary enzymatic digestion but secondarily by enzymatic attack on a reduction product, as shown for the clothes moth. In culture mediums, the usual source of nitrogen is a peptone. All peptones are complex, containing inorganic compounds, variable amounts of amino acids, protein split products and other substances with growth-producing capacities. Mosher, Saunders, Kingery and Williams found that Trichophyton gypseum would not grow on a medium containing only inorganic nitrogen. Successful growth in a synthetic medium was possible only if amino acids were added. These authors, as well as Robbins and Ma, determined that a suitable mixture of amino acids promoted growth better than a single amino acid. The latter authors found that the fungus could

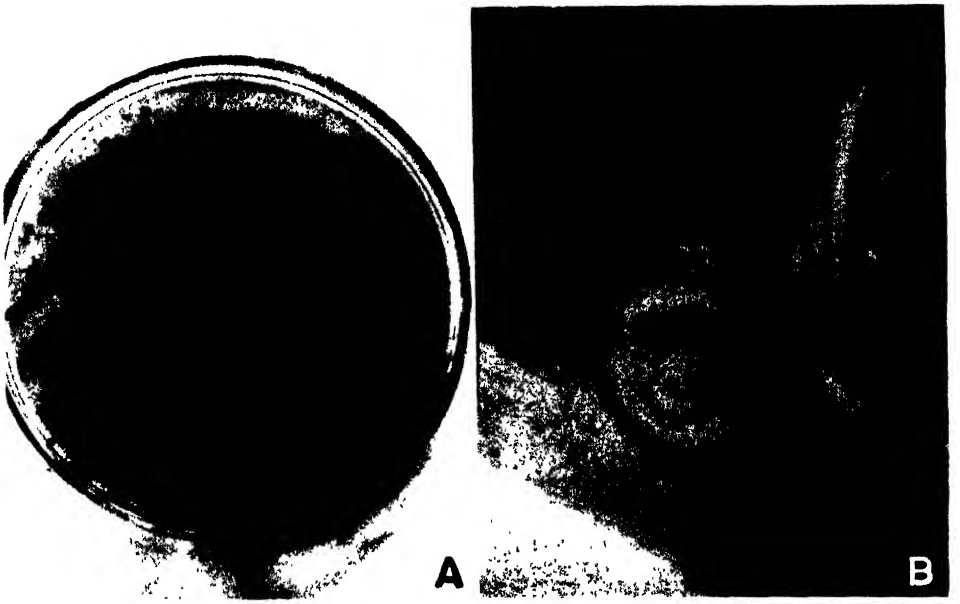


FIG. 2. Comparison of variations in growth of fungi in artificial medium and on human skin. *A*, Aspergillus species growing on corn meal agar. Successive rings of spores are due to variation in nutritional opportunities. In *B*, three distinct rings are present in lesion infected with M. lanosum. It is suggested that the formation of rings may be due to nutritional factors rather than to an allergic phenomenon as commonly supposed.

transform a single amino acid, such as asparagine, into other amino acids as necessary to synthesize its proteins. Growth is faster when a mixture of amino acids is available. According to Nickerson and Williams, an oxidative deamination process results in the production of ammonia from amino acids; this explains the increasing alkalinity of cultures of dermatophytes.

It is of interest that a highly virulent species of fungus, such as C. immitis, is no more exacting in its nutritional demands than ordinary contaminants such as species of Aspergillus or Penicillium. As a matter of fact, the growth factor requirements of all types of micro-organisms are very similar.

6. CARBON REQUIREMENTS

Goddard added various sugars to a 1 per cent aqueous solution of peptone and later measured the increase in dry weight of the inoculated fungus growth. He found that T. gypseum utilized dextrose, fructose, maltose, mannose and galactose but not lactose, whereas M. lanosum could not assimilate lactose or galactose.

7. OTHER NUTRITIVE NEEDS

Requisite for growth or reproduction are traces of many of the minerals, such as ammonium, potassium, calcium, magnesium, zinc, iron, copper, manganese, phosphorus and sulfur. For some fungi, thiamine is a requirement for growth; biotin occasionally stimulates growth. As shown by Benham, oleic acid is a necessary ingredient of the culture medium when Pityrosporum ovale is cultivated. The hydrogen ion concentration may range between 5 and 7. In our standard dextrose agar, the pH is usually in the region of 5.6.

8. PIGMENT FORMATION

In our study on the production of pigment by certain fungi, such as Trichophyton purpureum and Microsporum lanosum, it was concluded that the pigment is a metabolic product. These fungi were found to synthesize pigment in the presence of certain monosaccharides with closely related structural formulas, such as dextrose, levulose and mannose. One disaccharide, mannitol, was useful. Pigment was not produced when the only sugars in the culture medium were galactose (a monosaccharide) and other disaccharides, trisaccharides and polysaccharides. According to Foster, the formation of pigment may depend to some degree on the amount

and kind of available minerals, iron, copper and manganese being particularly important. This subject is considered further by Nickerson (*Biology of Pathogenic Fungi,* Chapter 10).

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CHAPTER V

Methods of Diagnosis of Fungous Disease

THE procedures to be described are the chief methods by which it is possible to determine the presence of fungi in specimens, to identify species and to decide on their pathogenicity.

1. THE DIRECT EXAMINATION

This is the simplest and yet the most important single means of laboratory investigation. It is the first step in establishing a diagnosis. Its limitation is that it rarely permits one to identify species. The method consists in mounting specimens of skin, hair, nail scrapings, pus or exudate and examining them under the microscope.

2. CULTURAL METHODS

(a) GIANT COLONIES.—Material containing fungi, if planted on suitable culture mediums, yields characteristic colony growths. In many instances identification of species can be satisfactorily made in this way alone.

(b) CULTURE MOUNT (HANGING-DROP, SLIDE CULTURE).—The character of the spores and the presence of any vegetative variations can be studied. A small amount of material from a cultural growth is mounted and immediately examined or inoculated in a thin medium, which can be studied as growth progresses.

3. FILTERED ULTRAVIOLET RADIATION

The phenomenon of fluorescence may be used in the examination of patients to determine the presence of tinea capitis or of tinea versicolor. It may also be used in the study of fungus colonies.

4. CUTANEOUS TESTS

The use of fungus vaccines in diagnosis and treatment has not been entirely clarified. We believe trichophytin to be specific in that it denotes sensitization by infection with a dermatophyte. Not every patient with a fungous infection is sensitized, since many virulent fungi do not have the capacity to sensitize the skin. The test, then, is not always diagnostic, although it is specific. Oidiomycin elicits so many reactions that it is useless in diagnosis. The reactions to coccidioidin, blastomycin and sporotrichin are considered to be specific. The subject is dealt with in more detail in Chapter VI, "Immunity and Cutaneous Sensitization."

5. ANIMAL INOCULATION

In order better to establish the pathogenicity of a given strain of microorganism, inoculation of the fungus into various laboratory animals may be helpful. It may also be used to obtain pure strains of a fungus which is also pathogenic to animals. It is used chiefly when one is working with the deep fungous infections, if negative results are obtained from the direct examination or from cultures.

6. FERMENTATION TESTS

Hopkins and Iwamoto found that fungi of the ringworm group utilize certain sugars by a process of acid fermentation but do not ferment lactose, saccharose, xylose or l-arabinose. All of the saprophytes which they studied fermented one or more of these sugars. In a later study Hopkins and Iwamoto were able to divide fungi of the ringworm group into three classes, which were based on speed of fermentation. Castellani, Benham and others have classified the yeasts and yeastlike fungi according to their fermentation reactions.

7. AGGLUTINATION TESTS

These are useful in the identification of the monilias (Benham). Conant also uses the agglutination reaction as a diagnostic test for blastomycosis.

8. PRECIPITATION AND COMPLEMENT FIXATION TESTS

These are also used with certain of the rare mycoses. Greenbaum investigated the Kolmer complement fixation test as applied to a group of serums

obtained from patients who were suffering from a variety of superficial ringworm infections. The negative results showed the test to be valueless here and indicated that few or no antibodies develop in the course of superficial ringworm.

9. FUSION OF MYCELIUM

This method was devised by Davidson and his co-workers to establish the identity of an unknown species. Only strains of the same species will fuse with each other when myceliums of two or more species are allowed to mingle. The myceliums of two strains of M. lanosum fuse, but no fusion takes place between M. lanosum and Microsporum audouini.

10. HISTOLOGIC EXAMINATION

This reveals the nature of the reaction of the host to the invasion of the pathogenic micro-organisms. The fungi themselves are rarely seen. In the superficial chronic infections the lack of pathologic changes may be helpful in the differential diagnosis from other dermatoses. In the deep forms of infection, there is no specific picture and granulomatous changes are the rule. Moore showed the close similarity between tuberculosis and many of the deep invasive fungous infections. In the acute form of each, a highly inflammatory reaction occurs, often leading to abscess formation. In the chronic forms, there are granulomas containing giant cells arranged in tubercle-like formation and plasma, epithelioid, lymphoid and polymorphonuclear cells. In fungous disease there are usually fewer epithelioid cells and more plasma and polymorphonuclear cells than in tuberculosis.

In some cases, histoplasmosis may only be established by postmortem examination of internal organs or tissues.

11. THE THERAPEUTIC TEST

When the diagnosis cannot be definitely established but the clinical features point to a fungous disease, it may be considered expedient to institute therapy. Improvement of the disorder following fungicidal therapy is evidence that the disease is mycotic. We advise against beginning therapy before the diagnosis is established by recognized laboratory methods. It is thus frequently advisable to delay treatment for several days or even weeks.

12. AUTOINOCULATION

Recovery of a recognized pathogen from a characteristic lesion is sufficient to establish the organism as the cause of the infection. If the lesion is atypical, particularly if the isolated fungus is of a variety not usually patho-

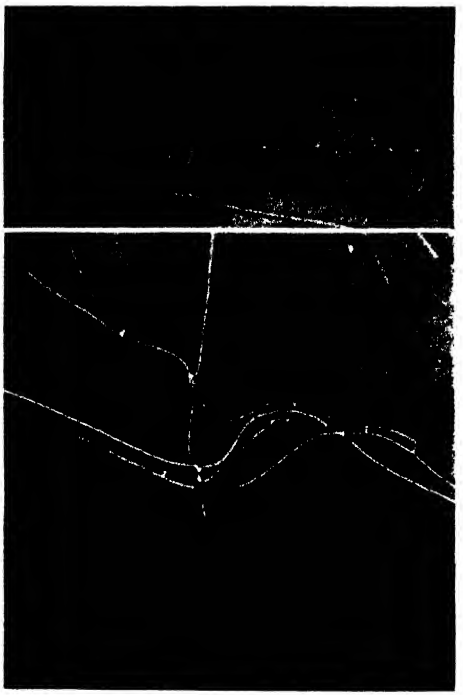

FIG. 3. Hyphal fusion between two strains of identical species. This does not occur when strains of dissimilar species are in proximity. *A*, T. gypseum. *B*, M. audouini. (*Courtesy of Harold Orr and Silver Keeping, Edmonton, Alberta, Canada.*)

genic or not usually isolated, further proof of pathogenicity is ordinarily required. Here the use of animals may be instructive but is not in itself conclusive, since variation in susceptibility with the species of animal shows that the response in human beings also varies. As mentioned by Weidman and others, the more frequent use of experimental autoinoculation is advisable. It is common knowledge that there is a considerable flora of contaminants, and it is possible that on occasion pathogenic strains may appear among them.

13. ROENTGEN EXAMINATION

This may give the first clue to the nature of the pathologic process. Pulmonary mycoses usually affect the base of the lung, and cavitation is

not commonly found. Metastatic growths in the bony framework may be detected.

14. EXAMINATION OF SPINAL FLUID

The routine inoculation of all specimens of spinal fluid on a suitable culture medium is advisable in all cases in which symptoms referable to the nervous system are present. It may be noted that the diagnosis of torulosis is rarely proved ante mortem. The chief reason is that the syndrome is not well delineated, but undoubtedly a contributory factor is the unawareness of physicians.

15. CLINICAL SYMPTOMS AND SIGNS

Perhaps the most important diagnostic aid of all is the clinical knowledge of the symptoms and signs of the invasion of pathogenic fungi.

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CHAPTER VI

Immunity and Cutaneous Sensitization

1. THE TRICHOPHYTIN TEST

AT THE outset it should be mentioned that a most welcome method for the diagnosis of a fungous infection would be a test based on specific acquired cutaneous sensitization to a fungus after infection. While sensitization often occurs shortly after infection, it does not do so invariably, and cutaneous tests based on the assumption that the phenomenon is constant often cause confusion. Since sensitization may have been produced by a previous infection, a test based on its demonstration cannot be regarded as unqualifyingly diagnostic. An eruption which is caused by fungi or their products and is due to cutaneous hypersensitivity is designated in this book as dermatophytid. Further discussion of the subject will be found on pages 58 and 116 to 119.

Most of the work in this field has been done with trichophytin, made from common dermatophytes. Oidiomycin, made from Monilia albicans, has also been investigated, and coccidioidin and sporotrichin are said to elicit specific reactions in patients infected with Coccidioides immitis and Sporotrichum schencki, respectively. According to Martin and others, patients with blastomycosis may or may not react to an extract made from Blastomyces dermatitidis. Negative reactions to the extract are always found in normal individuals.

Because of the controversial nature of the subject and because we believe that knowledge of previous investigations of allergic and immunologic phenomena relating to fungous disorders may assist in the development of better methods of diagnosis and treatment, we have here reviewed the literature somewhat more extensively than for some other subjects treated in this work.

(a) REVIEW OF THE LITERATURE.—In 1902 Neisser and Plato made an extract of fungi isolated from patients with ringworm and called the product "trichophytin." They found that when this substance was administered

by injection into a patient who was suffering from a deep-seated fungous infection, a general reaction resulted, with malaise, a rise of temperature and a local erythematous response at the site of the injection. No reactions occurred in normal persons or in patients with superficial fungous infections. They also prepared an extract of Achorion schoenleini, but patients with favus did not react to this or to trichophytin.

Bloch inoculated animals with Achorion quinckeanum and Trichophyton gypseum and showed that an animal so infected recovered spontaneously. The animal was then immune for as long as a year and a half and during that time could not be infected by either of the fungi just mentioned. The animals all exhibited a hypersensitive response to trichophytin. Bloch found that immunity could not be obtained except by cutaneous inoculation; it did not result from subcutaneous or intraperitoneal injection. Bloch and Massini found that immunity was obtained only from the inoculation of the living organism which produced an actual infection. Injection of trichophytin and favin (an extract of A. schoenleini) did not confer immunity, nor did the animal become hypersensitive. Bruhns also found that the inoculation of A. quinckeanum or T. gypseum caused immunity, while the injection of some other fungi in culture did not. Bruhns and Alexander confirmed the work of Bloch and found that fungi which produced deep-seated lesions had a greater power to immunize than those which produced superficial infections. The difference may have been partly due to the individual reaction, since the same fungus could produce a deep infection in one person and a superficial glabrous infection in another. Immunity was produced in the former but not in the latter instance. Citron failed to confirm the work of Neisser and Plato and did not observe any cutaneous reactions following the administration of trichophytin, even in the cases of patients with deep-seated ringworm infection.

Kusunoki was able to produce immunity in guinea-pigs with all types of fungi; this immunity was complete for any member of the same group of fungi. However, a strongly sensitizing fungus was capable of immunizing against all fungi, while the weaker infections did not prevent subsequent infection with a virulent fungus. He had more difficulty in producing immunity in rabbits than in guinea-pigs. He found that immunity may be transferred to the offspring when the mother is immune before conception or during pregnancy and that immunity is relative and not necessarily absolute.

Prytek found that after the infection of guinea-pigs with fungi, further inoculations produced either a modified form of the disease or no manifestations. Truffi noted the invariable response to the subcutaneous injection of trichophytin in patients with a deep-seated infection. Lombardo con-

sidered that a second infection following a deep infection was an allergic reaction due to the previous sensitization of the skin. Lombardo could not produce allergy by the injection of trichophytin. An attack of the disease was necessary to cause sensitization and immunity. Saeves also found that Epidermophyton inguinale and M. audouini had little power to sensitize the skin. He was able to find these fungi on the skins of inoculated animals 10 to 15 days after inoculation. This showed that the rapid death of the fungus was not the cause of its nonpathogenicity. These experiments indicated that a carrier of nonsensitizing fungi may pass the infection to another person without exhibiting a visible cutaneous reaction. Saeves inoculated guinea-pigs intracardially with suspensions of fungi and produced widespread cutaneous eruptions when the infecting fungus was A. quinckeanum or T. gypseum. No lesions appeared after the injection of A. schoenleini and E. inguinale. Sabouraud also found that guinea-pigs inoculated with different ringworm fungi became sensitized and remained so. Ribbert injected Aspergillus intravenously into rabbits. When spores of Aspergillus were then injected into the anterior chamber of the eye, less reaction occurred than in rabbits not previously so inoculated. According to Martenstein, the skin cells and the blood serum of a guinea-pig infected with A. quinckeanum contained certain specific bodies. If these were brought into contact with spores of A. quinckeanum in vitro, a toxic substance was produced. When injected, this produced a local inflammatory nodule. Martenstein showed that A. quinckeanum produced a specific antibody, first present at the site of the injection and later in remote areas of skin. If fungous elements were injected and came in contact with the specific antibody and with the resultant toxin, an inflammatory reaction was produced.

The nature of the trichophytin test was studied by Bloch, who sensitized himself to trichophytin by inoculation with a fungus. A piece of his skin and a piece of skin from a nonsensitized person were used in a graft to cover an ulcer of the leg of another subject who was not hypersensitive to trichophytin. Subsequent trichophytin tests elicited a reaction on the skin taken from Bloch but not on that from the control or on that from a remote area of skin of the recipient. This revealed a sensitivity of the skin cell itself as the basis for the immune reaction.

Bloch found that the trichophytin reaction appeared seven to eight days after infection with a fungus. Peck, in an experimental reproduction of tinea pedis with a downy type of T. gypseum, found that a reaction to trichophytin could be elicited 13 days after the inoculation of the organism. Amberg noted that the test may produce a positive reaction long after the disease has become cured and cited a case in which sensi-

tivity was retained for 29 years after a deep tinea infection. Amberg also noted a reaction delayed as long as eight days after the test was made. Bloch regularly obtained positive skin reactions in patients with kerion and also in those with tinea barbae. He found that the more inflammatory the disease, the greater the reaction to trichophytin. The superficial tinea infections gave slight or no reaction. Hanawa found that animals immune as the result of a previous infection exhibited well marked reactions to trichophytin. Bruck and Kusunoki found that the intensity of the reaction gradually decreased when trichophytin was repeatedly injected intracutaneously. Normal subjects always gave a negative reaction to this substance. Sutter, Amberg and Kusunoki each reported the occasional occurrence of a positive reaction in persons free from any type of ringworm. Low questioned the type of reaction in subjects free from fungous infection, suggesting that in these cases the reaction was nonspecific. Bloch warned against the possibility of pseudoreactions, which occasionally occur unless the proper technic is followed. Sutter demonstrated that the number of positive reactions to trichophytin increased with age. According to Sutter, the reaction to the trichophytin test is negative during attacks of pneumonia, scarlet fever, measles or typhoid fever but may be positive subsequently. During chronic diseases, no change in the reaction to trichophytin from that experienced by normal persons may be expected. In cachexia, the reaction may be absent. The reaction to trichophytin was also less on a paralyzed than on a normal limb. Scholtz stated that he obtained a few false positive reactions and found that the reaction to trichophytin was also positive in lupus vulgaris. This observation has not been substantiated by others. Patients with lupus vulgaris, pityriasis rosea and other diseases of the skin may also harbor a fungous eruption or may have been previously sensitized by such an infection.

Fuhs obtained a positive reaction to trichophytin in deep ringworm but not in the superficial varieties. Pedersen demonstrated that the test gave a stronger reaction on the abdomen, a common site for the development of trichophytids, than elsewhere. Pedersen and also Sutter found that a heightened reaction to trichophytin was obtainable in areas around active fungous lesions rather than at more remote sites. Arnold found 14 positive reactions in 130 healthy children with no history of ringworm. He also found that 58 per cent of children with superficial ringworm infection reacted to trichophytin. Many of the superficial infections gave more marked reactions than the deep infections. Arnold confirmed the work of Sutter, observing that the reaction to trichophytin was diminished or absent during eruptive fevers, and also agreed with Bruck and Kusunoki that a diminution in the strength of the reaction results from repeated

injections of trichophytin. Wise and Sulzberger also noted this phenomenon. Arnold considered trichophytin less specific than tuberculin but more specific than some bacterial products. Stein found that patients with favus failed to react to trichophytin. Low obtained only two positive reactions in 26 cases of proved ringworm infection and was disappointed in the results. He used vaccines made from strains of Microsporum, Trichophyton and Achorion. His positive results were obtained in a case of Microsporum infection of the scalp and in a case of favus. Negative reactions were obtained in cases of kerion and of tinea barbae.

It was noted by Walthard and by Jadassohn and Peck that patients with allergic secondary eruptions (dermatophytids) regularly reacted to trichophytin. Sulzberger and Lewis demonstrated that in some persons an eczematous reaction was obtained to a patch test with trichophytin. Rosen, Peck and Sobel, who studied the reaction to trichophytin in 102 patients, concluded that the test was specific. They compared the relative merits of the intracutaneous, scratch and patch tests and found the intracutaneous test to be the most reliable. No cultural studies were undertaken.

Van Dyck, Kingsbury, Throne and Myers reported the cases of 100 patients who presented eczematous eruptions and others which suggested fungous infections. In each instance the reaction to a commercial extract of trichophytin (Metz) was positive. They used a 1:10 dilution, whereas we later found that a 1:100 dilution of the same extract was capable of producing reactions in susceptible subjects. Van Dyck and his associates inferred that the reaction to trichophytin may displace other methods in the diagnosis of fungous infections. It was later reported that 117 of 317 subjects had positive reactions to trichophytin similar to those previously reported. Although not specifically stated, it was implied that the remaining 200 subjects also exhibited positive reactions. The presence of a positive reaction was held as the diagnostic equivalent of demonstration of the micro-organism. The high concentration of trichophytin (1:10) used as testing material and the absence of cultural studies, as well as the lack of a suitable number of patients as controls, weaken the value of these reports.

Williams and Carpenter evaluated trichophytin in diagnosis and reported that the reaction was positive in 51 cases of clinical fungous disease in 36 of which there was microscopic verification. There was a negative reaction to the test in 19 cases of clinical fungous disease, in five of which the microscopic test gave positive results. In 36 control subjects, clinically free of fungous disease, there was only one positive reaction to trichophytin, and this could not be accounted for by the history or the physical findings. Williams and Carpenter stated that false positive reactions to trichophytin

may occur if the extract is contaminated with bacteria. They noted that many superficial tinea infections gave positive reactions. Although other authors noted a reaction to trichophytin in patients who also had pityriasis rosea, they were unable to confirm this observation. They concluded that "intradermal tests with trichophytin are an aid in diagnosing mycoses of the glabrous skin." Later Williams reported that "the trichophytin test appears to be specific and on careful examination of the patient and of his history exceptions are usually found to be only apparent." Sulzberger and Wise stated that an overwhelmingly large majority of patients who have trichophytids react to the intradermal injection of trichophytin with an inflammation not to be observed in normal persons who have had no prior contact with fungi. They warned against relying on the test as a positive means of identifying an eruption on the hands, since the reaction may be positive because of a prior infection or an infection in another part of the body. The specificity of trichophytin when compared with oidiomycin was demonstrated by Sulzberger, who injected serum from a patient who was known to have circulating antibodies into the skin of normal young women who were previously without sensitiveness. The sites were then tested, and reactions were obtained to trichophytin but not to oidiomycin.

Pels and Schlenger used trichophytin in testing 230 subjects. They found the reaction to be positive in 83 per cent of 65 patients who showed the clinical characteristics of the disease. Of 165 subjects who were clinically free of the disease, 35 per cent had positive reactions. In some of the cases fungi were demonstrated. Pels and Schlenger were not entirely convinced that trichophytin is specific in its effect.

Muskatblit and Director made their own trichophytin and tested 350 patients. Of 49 patients with fungous infections proved by culture, 41 had positive reactions and eight no reaction. The results of the tests were as follows: Epidermophyton interdigitale, 22 positive, one negative; Epidermophyton rubrum, six positive, three negative; E. inguinale, three positive, none negative; M. lanosum, seven positive, one negative; Trichophyton violaceum, two positive, none negative; T. gypseum, one positive, none negative; A. schoenleini, one positive, one negative; Microsporum minutissimum, none positive, one negative. These authors warned against "depot" reactions in which the response was not greater than the original injection of material.

Goodman and Marks used the nitrogen content of trichophytin and various bacterial products as the basis for their standardization. They found that when like amounts of the antigens, on the basis of this standardization, were administered intracutaneously, some patients reacted indis-

criminately but most showed a selectivity of response. They found that boiling had no effect on the potency of trichophytin (thermostability). In a group of unselected subjects, those who gave a negative reaction to tuberculin also failed to react to trichophytin. In some of the cases in which there were negative reactions to trichophytin, however, positive reactions to old tuberculin were produced. Otherwise no correlation between the two allergens was noted. Intradermal injection of trichophytin over the site of a subcutaneous injection elicited a stronger reaction than intradermal injection alone. The presence of phenol in the amount usually added as a preservative had no influence on the local reactions to any of the antigens used.

Robinson and Grauer pointed out that a given eruption is not necessarily proved to be of fungous origin because the trichophytin reaction is positive. They also observed a number of cases of mycotic infection in which the reaction was negative. This finding was in agreement with the findings of others. A possible source of error in the work of Robinson and Grauer was that many of the fungi which they considered the cause of infection were common laboratory contaminants and as such not usually considered of pathogenic significance.

Tomlinson obtained uniform reactions after the use of various kinds and mixtures of trichophytin. Sulzberger, Lewis and Wise in a comparison of three types of commercial trichophytin found a fairly uniform response to their use. There was, however, no correlation in number or degree between reactions to trichophytin and reactions to oidiomycin, showing that Trichophyton and Monilia belong to different immunologic groups of fungi, each capable of producing its independent specific hypersensitivity. Peck stated that a positive reaction to trichophytin must be present before a diagnosis of trichophytid may be determined. Traub disagreed with Peck, stating that he had observed cases of typical dermatophytid in which reactions to trichophytin were negative. Traub and Tolmach had previously expressed their lack of confidence in trichophytin as a diagnostic or therapeutic aid, doubting its specificity. They found no relation between the severity of the infection and the cutaneous responses to injections of trichophytin. In seven cases in which there were demonstrable fungi on the feet and vesicular or squamous lesions on the hands, which they called epidermophytid, negative responses to trichophytin were obtained.

Knierer concluded from cutaneous tests of 115 persons that trichophytin has some diagnostic value provided it is employed with due criticism. He found the reaction to be positive in 10 to 35 per cent of persons free from mycotic disorders and negative in 25 to 45 per cent of patients who had a mycosis.

W. Jadassohn, Schaaf and Wohler and their collaborators found the uterine horn of a guinea-pig (Schultz-Dale technic) to be capable of sensitization to products of fungi. Anaphylactoid shock followed the intracardial injection of desiccated trichophytin in a sensitized animal one month after the sensitizing injection. Utilizing the Schultz-Dale phenomenon, these workers found that the extracts prepared from various species of dermatophytes all showed a common antigenic factor and that, in addition, each species contained several other antigenic factors not found in other species. Antigens characteristic of each species were present, and there may have been another antigen common to two or more species.

A number of cases of immediate wheal reaction to trichophytin have been reported. These were mentioned by Marcussen, who summarized the evidence that the reaction to trichophytin is specific. He reported eight cases in which there was an immediate wheal reaction at the site of the intracutaneous test with trichophytin. In six cases there was either a family history of allergic disease or the presence of such a disease in the subject. Both this factor and the presence of prolonged deep mycosis, often with hematogenous spreading, were considered by Marcussen to be important factors in the production of the immediate wheal reaction. He stated that a mycotic infection was capable of giving rise to the formation of two different antibodies. One of these circulated in a patient with allergic manifestations or history, while the other was a sessile antibody which might be present in any person but was often absent in patients with allergic diseases. Both antibodies were directed against the same antigen component. Thus, in the case of patients showing an immediate wheal reaction, there was diminution or complete absence of a delayed reaction, since the antigen was consumed in whole or in part by the other antibodies. No local desensitization followed the wheal reaction, since the injection of trichophytin in sites previously used for Prausnitz-Küstner experiments resulted in the same strength of delayed reaction normally present. Marcussen stated that a patient is seldom inspected immediately after an injection of trichophytin. For this reason the immediate reaction is apt to be overlooked. Marcussen mentioned that Bernton and Thom found 12 cases of immediate wheal reaction among 400 patients. Marcussen was able at times to transmit the susceptibility by means of passive transfer, which usually was not possible with serum from patients who exhibited the more usual delayed reaction.

In a series of over 400 patients Lewis, Sulzberger and Wise observed six instances of a flare-up reaction seven days after a test dose of trichophytin, in a site where no reaction was present at the end of 48 hours. When these patients were retested with trichophytin, reactions appeared within 48 hours.

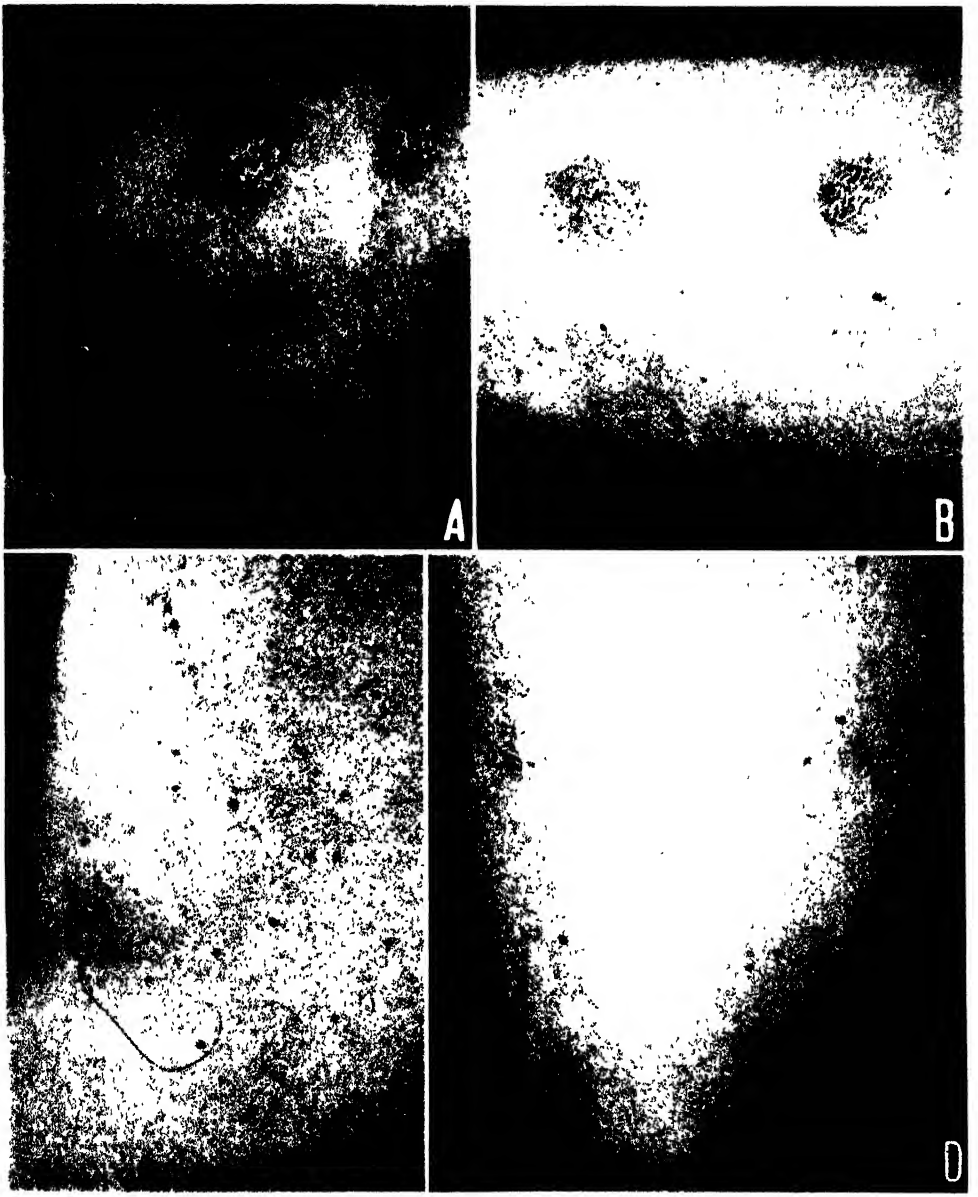

FIG. 4. Specific reactions following intracutaneous test doses of fungus vaccines. *A* and *B*, the usual eczematous type of reaction after 48 hours, showing similar responses to different brands of trichophytin. No reactions resulted from the tests with antigens of other microorganisms. *C*, immediate wheal type of reaction observed 10 minutes after the injection of trichophytin, showing the irregular wheal of a size greatly increased over that produced by the injected fluid. A control injection of saline solution elicited a negative response. *D*, the site of an immediate wheal response shows no visible reaction when observed after 48 hours.

The authors did not consider it proved that specific acquired sensitization to fungi was due to the test injections of trichophytin, although such a possibility was suggested.

We found that in children with no obvious fungous infection a negative reaction to trichophytin was the invariable rule. When a fungous infection was present, the reactivity of the skin to trichophytin varied according to the species of infecting organism. Eight children whose scalps were infected with A. schoenleini or T. violaceum showed negative reactions to the intracutaneous test with trichophytin. In seven of 27 children whose scalps were infected with M. audouini there was a reaction to trichophytin, but in only one instance was a 4 plus reaction noted. In the remaining 20 children the response was negative. When M. lanosum was the infecting organism, the result of the intracutaneous test was usually positive. The test was considered helpful in determining the prognosis and the type of therapy to be employed. If the reaction to trichophytin was negative, the time for cure was usually prolonged, whereas a vigorous reaction was frequently followed by a rapid clinical response to treatment.

(b) SPECIFICITY OF THE TRICHOPHYTIN TEST.—The work of the older investigators repeatedly showed that after deep infections with fungi, the cutaneous test with trichophytin invariably invoked a cutaneous response, which could be elicited for many years thereafter. Marcussen pointed out that (1) trichophytin did not possess a primary toxic effect, (2) reactions were not caused by hypersensitivity to the culture medium or its components and (3) the commercial extract and a monovalent vaccine made from T. gypseum (fluffy) caused the same or similar reactions. All these points favor the belief that the reaction to trichophytin is specific. Sulzberger and Kerr and later Sulzberger, Lewis and Wise showed that patients did not react in a uniform manner to both oidiomycin and trichophytin and that sensitization to one extract did not necessarily bring about sensitization to the other. In further support of the opinion that the reaction to trichophytin is specific are the figures in Tables 1, 2 and 3. We have recorded reactions in 70 patients. The patients listed in Table 1 were considered to have trichophytid, and all revealed a strong reaction to trichophytin. The patients represented in Table 2 were selected because they reacted strongly to oidiomycin and cultural examinations showed M. albicans. The patients listed in Table 3 reacted strongly to catarrhal vaccine. The dissimilarity in both the number and the strength of the reactions to these three extracts in all three groups is at once apparent.

(c) IS THE SPECIFICITY OF THE TRICHOPHYTIN TEST DETERMINED BY SPECIES OR GENUS?—The work of W. Jadassohn, Schaaf and Wohler showed that the antigen in trichophytin which elicits the reaction is not a single sub-

TABLE 1.—Reaction to Oidiomycin and Catarrhal Vaccine of Patients with Strong Reaction to Trichophytin*

Patient	Trichophytin		Oidiomycin		Catarrhal Vaccine	
	48 Hr.	1 Wk.	48 Hr.	1 Wk.	48 Hr.	1 Wk.
B.J.	+++	+++	+	++	O	O
W.A.	++	+++	++	+	+	O
A.T.	++	++	++	+	++	++
L.I.	++	++	±	±	±	±
S.N.	++	++	+++	±	O	O
T.R.	++	++	+	±	±	±
S.M.	++	++	++	+	+	O
S.J.	++	+	+++	O	+	O
G.E.	+++	++	+++	+	++	±
G.B.	++	+++	++	+	+	O
C.A.	+	+++	+++	++	±	±
P.A.	+	++	+++	+	O	O
H.J.	+++	+++	+++	±	±	O
W.H.	++	++	+++	+	O	O
W.A.	+	++	+++	+	±	O
H.C.	++	++	+++	++	±	O
M.H.	++	++	++	+	±	O
F.W.	++	++	+	+	+	±
G.G.	++	++	±	+	±	O
M.I.	++		+++		++	
C.W.	++	++	+	O		
A.M.	++	+	O	O		
F.E.	+	+	++	±	±	O
S.C.	++	+	++	O	+	O
B.B.	++	+	+	+		
Total patients 25						
Total positive reactions	25	24	22	15	9	1

*For all patients, cultural examination yielded fungi.

stance common to all species of Trichophyton but that each species has a component peculiar to itself. However, the greatest portion of the extract is undoubtedly the same, no matter what the source of the extract. In testing we have used monospecies extracts made from M. audouini, M. lanosum, Trichophyton purpureum and T. gypseum and are able to substantiate the conclusion of Tomlinson and others that a patient who reacts to one type of trichophytin will usually also react to a type made from another species. Thus patients whose skin was sensitized by an infection with T. gypseum had a comparable response when the skin was tested with extracts

of T. gypseum and of T. purpureum. Conversely, patients with infections due to T. purpureum who did not react to an extract made from that organism failed to react to a vaccine made from T. gypseum. Similarly, one may observe the variations (usually minor) which occur when two commercial trichophytins are administered to the same patients. A study of

TABLE 2.—Reaction to Trichophytin and Catarrhal Vaccine of Patients with Strong Reaction to Oidiomycin*

Patient	Oidiomycin		Trichophytin		Catarrhal Vaccine	
	48 Hr.	1 Wk.	48 Hr.	1 Wk.	48 Hr.	1 Wk.
B.B.	+++	+	O	++	±	+
R.E.	+++	O	O	O	±	O
T.E.	+++	O	O	O	±	O
W.F.	+++	±	O	+	++	O
G.B.	+++	++	++	+	+++	++
A.Y.	+++	O	O	O	O	O
D.C.	++	±	O	O	+++	±
G.R.	+++	+++	±	+	++	±
S.I.	+++	+++	O	+	++	±
M.I.	+++	O	++	O	±	O
G.P.	+++	+++	+	+	O	O
S.E.	+++	+	+	O	O	O
D.J.	++	++	O	O	O	O
K.J.	++	++	±	±	O	±
S.J.	++	+	+	±	±	±
M.S.	++	±	+	++	±	O
D.A.	±	O	O	O	±	O
M.I.	++	++	O	O	O	O
D.R.	++	+	±	±	±	O
A.Y.	+	±	O	O	O	O
Total patients 20						
Total positive reactions	19	11	6	7	5	2

*For all patients, fungous examination showed M. albicans.

these variations has already been published but may be briefly referred to here. Of 57 reactions to one or more of three trichophytins, 53 (93 per cent) were elicited by Metz (1:100), 43 (75 per cent) by Lederle (1:30), and 25 (43 per cent) by Bischoff trichophytin (dermatomycol undiluted). After additional experience we noted agreement between the Metz and the Lederle trichophytin in 80 to 95 per cent of cases. It would appear that the specificity of the test is chiefly due to the component in the vaccine which is common to all members of the genus.

(d) INFECTION DOES NOT ALWAYS MEAN SENSITIZATION TO TRICHOPHYTIN.—Perhaps the lack of understanding of this fact has led to the belief of many physicians that trichophytin does not elicit specific reactions. Saeves noted that E. inguinale and M. audouini failed to sensitize the skin, and

TABLE 3.—REACTION TO TRICHOPHYTIN AND OIDIOMYCIN OF PATIENTS WITH STRONG REACTION TO CATARRHAL VACCINE*

PATIENT	CATARRHAL VACCINE		OIDIOMYCIN		TRICHOPHYTIN	
	48 Hr.	1 Wk.	48 Hr.	1 Wk.	48 Hr.	1 Wk.
J.H.	+++	±	++	+	O	O
K.M.	++	+	±	O	O	O
M.N.	+++	++	O	±	O	O
M.C.	+++	O	+	O	O	O
M.F.	+++	±	O	O	O	O
R.V.	+++	O	+	±	++	+
R.L.	++	++	++	++	O	O
M.E.	++	+	O	O	O	O
O.A.	+++	+	+	±	±	O
M.C.	+++	+	+	O	O	O
B.A.	+++	O	±	O	O	O
R.S.	+++	O	++	O	O	O
R.P.	+++	O	O	O	O	O
S.L.	+++	+	+++	+	O	O
B.S.	+++	O	+++	+	++	++
M.R.	+++	O	+++	±	O	O
R.M.	+++	O	+++	++	±	+
K.B.	+++	±	+++	±	++	++
G.B.	++	O	+	+	O	+
B.V.	+++	+	++	O	O	O
D.H.	+++	+	++	+	O	+
G.R.	+++		+		±	
A.A.	+++	+	++	±	O	O
S.I.	++	+	+	O	O	O
A.H.	+++	+++	+	+	O	++
Total patients 25						
Total positive reactions	25	12	19	8	3	7

*For all patients, fungous examination gave negative results.

Stein reported that patients with favus reacted negatively to trichophytin. Muskatblit and Director reported the reaction of a series of 48 patients with culturally proved fungous infection and noted a variation in the response according to the species of infecting organism. In Table 4 may be found our results in testing with trichophytin 254 patients who had

fungous infections. It is here shown that a patient with a severe infection may yield a negative response to trichophytin. When the infecting organism is T. purpureum or A. schoenleini, for example, there is little likelihood of cutaneous sensitization and response to therapy is usually poor. Another

TABLE 4.—Reaction to Trichophytin, after 48 Hours, of 254 Patients with Proved Fungous Infection

Fungus	No. of Cases	No. of Negative Reactions		No. of Positive Reactions			Percentage of Positive Reactions
		O	±	+	++	+++	
M. lanosum	39	4	5	15	14	1	76
M. audouini	48	18	15	8	7	0	31
A. schoenleini	10	7	1	2			20
T. purpureum	50	25	13	8	2	2	24
T. gypseum	88	13	12	35	23	5	71
T. violaceum	6	3		2	1		50
M. fulvum	4		1	1	2		75
T. niveum	4	1			3		75
E. cruris	3	1	1	1			33
T. crateriforme	2			1	1		100

possibility is that in a case of recent infection the test may be undertaken before sensitization has occurred. In experimental work, the time necessary for sensitization may vary between one and two weeks.

We have found that approximately 53 per cent of patients with infections due to T. purpureum who exhibited negative reactions according to

TABLE 5.—Comparison of Immediate and Delayed Reactions to Trichophytin for Three Species of Infecting Micro-Organisms

Fungus	No. of Cases	Positive Immediate—Negative Delayed, %	Both Positive, %	Negative Immediate—Positive Delayed, %	Both Negative, %
T. purpureum	100	53	32	10	5
T. gypseum	150	1.5	15	72.9	10.6
E. inguinale	19	15.8		26.3	57.9

examination of the test site after 48 hours showed a positive response when the site was examined 10 minutes after the test. An additional 32 per cent of patients reacted both after 10 minutes and after 48 hours (Table 5). In some instances this immediate wheal reaction is associated with circulating antibodies, as evidenced by passive transfer tests. In the other cases we are unable to demonstrate circulating antibodies. It is interesting that in the latter cases a second injection into the site of the first fails to elicit

any immediate response, whereas in the first group (with circulating antibodies) there is no difference between the responses to the first and those to a subsequent injection in the same site at various intervals between the two.

Our studies on this important subject of immediate wheal reactions have not been completed, but it seems that some so-called negative reactions may be attributed to a lack of observance of the immediate response. We have so far noted the wheal reaction not only in cases of infection due to T. purpureum but also in a few instances when only E. inguinale and T. gypseum have been found on culture. We have also observed an immediate wheal reaction to oidiomycin. In the cases in which there are no circulating antibodies, the sensitized tissue appears to be situated in the upper cutis with increased permeability of the capillaries of the skin.

(c) DOES A PATIENT WITH A TRICHOPHYTID ALWAYS REACT TO TRICHOPHYTIN?—It is theoretically possible that the vaccine (trichophytin) may lack some of the components of the living fungus which are capable of eliciting reactions. However, in practice such an occurrence must be rare. If the patient's skin is sensitized so that a trichophytid reaction is produced, it is hardly likely that it will fail to react to the extract. We subscribe to the principle that a positive reaction to trichophytin is requisite to a diagnosis of dermatophytid. Some observers have reported negative reactions to trichophytin in cases of typical dermatophytid. They state that they have demonstrated anticutins to trichophytin to explain the anergic phase. In

TABLE 6.—REACTION TO TRICHOPHYTIN TEST OF PATIENTS WITH ERUPTION ON HANDS AND FEET FOR WHOM CULTURE FROM FEET YIELDED T. GYPSEUM

	No. of Cases	No. of Negative Reactions		No. of Positive Reactions			Percentage of Positive Reactions
		O	±	+	++	+++	
Trichophytin							
Lederle 48 hr.	38	1	4	20	11	2	87
1 wk.	29	1	4	15	8	1	83
Metz 48 hr.	34	1	3	12	15	3	88
1 wk.	29	1	0	13	12	3	97

Table 1 are listed the cases of trichophytid in which we are reasonably certain that no other diagnosis could explain the rash. Our diagnosis was based on an evident inflammatory focus preceding the eruption and was proved by culture and by the subsequent development of vesicles which were sterile for the growth of fungi. Irritation of the original focus sometimes caused an exacerbation of symptoms; the test dose of trichophytin

always elicited a response (usually strong) and sometimes caused a focal reaction. In Table 6 are listed cases in which cultures of T. gypseum were isolated from the feet by culture and in which there was a concomitant eruption on the hands. Although some of these rashes were considered non-mycotic, it is interesting that in 87 per cent of the cases the test with trichophytin showed a positive reaction.

(f) VARIATIONS IN REACTIVITY TO TRICHOPHYTIN ACCORDING TO CLINICAL TYPE.—We find no difference in the reactivity of the skin to trichophytin between cases of inflammatory infections without evidence of trichophytid and cases of trichophytid. In all instances the patients react to the test. Likewise, all patients with acute tinea pedis due to T. gypseum

TABLE 7.—REACTION TO TRICHOPHYTIN TEST OF PATIENTS WITH ERUPTION ON FEET FOR WHOM CULTURE YIELDED T. GYPSEUM

	No. of Cases	No. of Negative Reactions		No. of Positive Reactions			Percentage of Positive Reactions
		O	±	+	++	+++	
Trichophytin							
Lederle 48 hr.	50	12	8	15	12	3	60
1 wk.	28	6	6	9	5	2	57
Metz 48 hr.	45	8	7	13	15	2	67
1 wk.	27	6	2	8	9	2	70

have positive reactions. The reaction to trichophytin in patients with infection of the feet due to T. gypseum is shown in Table 7. Only 60 per cent of these patients showed hypersensitivity to trichophytin. In the patients with infection due to T. gypseum but with a negative reaction to trichophytin either the cutaneous manifestation was a slightly inflammatory focus or the organism was isolated from an infected nail. We conclude, therefore, that some factor or factors are responsible for a trichophytid other than infection with a potentially sensitizing organism. Some of the factors which may precipitate a trichophytid are (1) heat, (2) severe trauma (to hands), (3) intense anxiety and (4) administration of penicillin. That a patient exhibits a positive reaction to trichophytin does not necessarily mean that a trichophytid will develop.

(g) "FALSE" POSITIVE REACTIONS.—We have not been able to confirm the statement of Tolmach and Traub that a false positive reaction may follow if one test site receives more than one test dose of trichophytin. To 10 patients who were not reactive to trichophytin, from two to five injections of trichophytin were administered at the same site at intervals of from two days to two weeks without evidence in any case of the development of

cutaneous sensitivity to the vaccine. We consider this an important observation, since it has been the experience of a number of investigators that the initiation of cutaneous sensitivity to fungi is only possible when the living organism invades the living tissues. The results of our tests seem to confirm this opinion. In another report it was noted that occasionally a tendency to a response had developed 48 hours after an initial delayed response to trichophytin. It was undecided, however, whether this tendency could be classified as initiation of sensitivity.

(h) GRADED TRICHOPHYTIN TESTS.—A small percentage of patients do not react to trichophytin even in concentrated solution (1:10 or undiluted), and another small group react to a highly dilute solution (1:300). In neither of these groups, which we have studied, do the patients have well defined clinical peculiarities or family histories of allergy, and we are unable to account for their different responses or as yet to attach any significance to the finding. With the largest number of persons trichophytin undiluted or in concentrated solutions (up to 1:10) is primarily an irritant, and more dilute solutions are requisite for determination of hypersensitivity or the lack of it. The optimal dilution varies somewhat with the product.

(i) THE PATCH TEST WITH TRICHOPHYTIN.—It has been known for a number of years that some persons react to a patch test with trichophytin. This has led to the belief that some of the eczematous eruptions on the hands may be toxic fungous eruptions (dermatophytids) or that the infection may be primarily eczematous, simulating contact dermatitis. Our studies in regard to this point are as yet incomplete, but from our observations to date we conclude that both possibilities must be uncommon. In our experience the patch test with trichophytin has less significance than the intracutaneous test. Even in cases of undoubted dermatophytid the patch test with trichophytin frequently shows a negative reaction. This may be interpreted to mean that in these rashes the epidermis is not the tissue primarily sensitized.

(j) DOES THE SITE OF INJECTION OF TRICHOPHYTIN INFLUENCE THE SIZE OF THE RESPONSE?—When the arm, the leg and the abdomen were used for test sites no appreciable difference was noted in the size of the reaction, nor did we find one site reactive when one or more of the others were nonreactive. In some instances a moderate increase in the size of a reaction was noted when skin adjacent to an active fungous infection was tested and the reaction was compared with that in skin at a remote point. This, however, was not invariable, and we have even noted a diminution in the size of the reaction near an active fungous focus. In routine practice the upper, outer arm is the usual test site.

(k) RELIABILITY OF THE INTRACUTANEOUS TEST WITH TRICHOPHYTIN.—We

have found that when the trichophytin test is employed as part of a thorough study of the case, including clinical and other laboratory examinations, it is of confirmatory value both in diagnosis and in prognosis. It has been said that the test cannot be useful in diagnosis since it simply denotes sensitization to a dermatophyte, which may have occurred at a previous time and thus have no significance in connection with a given eruption. The second important disadvantage of the test is the undisputed fact that it may produce a negative reaction in a patient from whose skin pathogenic fungi have been isolated. Finally, the correlation of positive reactions and a presenting dermatosis should be carefully interpreted, both as to existing probabilities and as to the presence of an active inflammatory fungous disease in the past.

It is our belief that the first criticism is not altogether founded on accurate clinical or laboratory proof. It is probable that an inflammatory response to a fungous infection is necessary before the skin becomes sensitized. A careful study of the history for rashes will determine whether such an eruption previously occurred. A thorough search usually reveals traces of the condition, since spontaneous cure of most fungous diseases is rare. Microscopic and cultural studies will aid in the appraisal. If the examination is thorough, few instances of inability to interpret the results of the test will occur. We do not believe that the test can take the place of other investigations, such as the cultural determination of the pathogenic micro-organism, but it may yield information which cannot otherwise be elicited.

The reason for the seeming unreliability of the test in the face of proved fungous infection has already been explained (Table 4). Such a fungus as A. schoenleini has a low sensitizing index, while one like T. gypseum has a high index. Few patients having favus react to trichophytin; with T. gypseum infection such a reaction is usual.

(1) INTERPRETATION OF THE INTRACUTANEOUS TEST WITH TRICHOPHYTIN.—When a pathogenic fungus is isolated, a positive reaction to the test is additional evidence that an eruption at a remote point is also fungous. In cases in which the response to trichophytin is vigorous the prognosis is favorable. A strong reaction to the test should lead to conservative methods of treatment, such as application of bland wet dressings, soaks, powders, soothing lotions, pastes or ointments, and when there is exudative dermatitis the use of roentgen rays may be considered. In a small percentage of cases, the reason for the development of cutaneous sensitivity to trichophytin cannot be determined from the history, the examination or concurrent laboratory investigation. Of 111 patients who presented inflammatory eruptions on the feet but no other rashes and for whom the microscopic and

cultural tests yielded negative results, from 50 to 58 per cent showed a positive reaction to trichophytin. In many of these cases previous treatment had masked the infection and made the isolation of fungi difficult. In others the primary disorder was definitely determined to be nonmycotic. The test was of little value for this series of patients, except that a doubtful

TABLE 8.—Reaction to Trichophytin Test of Patients under 20 Years, Examination for Fungi Having Given Negative Results

		No. of Cases	No. of Negative Reactions		No. of Positive Reactions			Percentage of Positive Reactions
			O	±	+	++	+++	
Trichophytin								
Lederle	48 hr.	106	79	11	9	5	2	15
	1 wk.	75	61	3	8	3	0	15
Metz	48 hr.	105	74	15	12	2	2	15
	1 wk.	75	60	5	5	5	0	13

reaction to trichophytin led us to repeat the cultural studies. Of 106 patients under 20 years of age who had rashes which were not considered fungous, only 15 per cent reacted to the trichophytin test (Table 8). We therefore wish to stress the diagnostic value of a positive reaction to trichophytin in children and young adults. In tests of 45 patients over 50 years of age who

TABLE 9.—Reaction to Trichophytin Test of Patients over 50 Years, Examination for Fungi Having Given Negative Results

		No. of Cases	No. of Negative Reactions		No. of Positive Reactions			Percentage of Positive Reactions
			O	±	+	++	+++	
Trichophytin								
Lederle	48 hr.	45	20	11	9	4	1	31
	1 wk.	39	16	10	9	4	0	33
Metz	48 hr.	45	18	11	10	5	1	35
	1 wk.	39	18	10	7	4	0	28

were clinically free of fungi, 31 to 35 per cent of the reactions were positive (Table 9), over twice the percentage of patients under 20 years. The possibility of error therefore increases with age. In tests of 77 patients of miscellaneous ages with various cutaneous disorders not considered to be mycotic, from 16 to 20 per cent of the reactions were positive (Table 10). In a series of 216 cases in which an eczematous eruption was confined to the hands and in which incidental examinations for fungi on both the

hands and the feet gave negative results, only 20 per cent of the patients showed a positive reaction to trichophytin (Table 11). It is interesting to note that for all 557 patients for whom fungous examinations gave negative results, the incidence of the reaction to trichophytin was approximately 29

TABLE 10.—Reaction to Trichophytin Test of Patients with Miscellaneous Eruptions, Examinations for Fungi Having Given Negative Results

	No. of Cases	No. of Negative Reactions		No. of Positive Reactions			Percentage of Positive Reactions
		O	±	+	++	+++	
Trichophytin							
Lederle 48 hr.	77	46	19	7	5	0	16
1 wk.	53	34	7	8	4	0	23
Metz 48 hr.	76	45	16	9	6	0	20
1 wk.	53	33	9	7	4	0	21

per cent. In half of these cases the clinical evidence suggested mycotic infection.

Since we believe the test to be specific in the majority of instances and have noted that patients with primarily inflammatory eruptions proved by culture to be fungous inevitably show positive cutaneous reactions to

TABLE 11.—Reaction to Trichophytin Test of Patients with Eruption on Hands but Not on Feet, Examination for Fungi Having Given Negative Results

	No. of Cases	No. of Negative Reactions		No. of Positive Reactions			Percentage of Positive Reactions
		O	±	+	++	+++	
Trichophytin							
Lederle 48 hr.	216	129	42	32	12	1	20
1 wk.	141	90	23	14	13	1	20
Metz 48 hr.	205	121	43	24	15	2	20
1 wk.	135	80	18	23	12	2	28

trichophytin, we believe that a positive reaction is of value but a negative reaction of even greater value when one is trying to decide whether an inflammatory eruption is of mycotic origin. If the rash is of several weeks' duration (which would allow ample time for sensitization), if neither microscopic nor cultural studies show fungi and if the intracutaneous test to trichophytin gives a negative result, an exudative inflammatory eruption may be declared to be nonmycotic.

2. THE OIDIOMYCIN TEST

In an investigation (in which Royal Montgomery collaborated) of the test with oidiomycin, a commercial vaccine made from M. albicans, we concluded that the information obtained from the test was rarely useful. Sensitization of the skin might occur from a focus in the intestinal tract or from a lesion which had subsequently resolved. Of 42 patients having some form of localized cutaneous moniliasis, a positive response to the test was noted in 57 per cent. Of 91 patients with an infection due to a fungus other than M. albicans, 45 per cent showed a positive reaction, while of 192 patients with no evidence of any type of fungous infection, 46 per cent reacted. In a second series of tests M. albicans was found to be present in cultures of material from the tongue, skin or stool of 52 of 100 patients. The test produced a positive reaction in 58 per cent of the patients with positive cultures and in 54 per cent of those with negative cultures; the similarity of results is noteworthy.

From these findings, which substantially agree with those of Biberstein and Epstein and of Staehelin and his co-workers, it is obvious that the test has no practical value in the diagnosis of infections due to M. albicans. We advise that the oidiomycin test be abandoned.

3. OTHER CUTANEOUS TESTS

We came into the possession of a supply of coccidioidin through the courtesy of the late Ernest C. Dickson, of Stanford University, and have tested the cutaneous sensitivity of over 400 patients who had various dermatoses, many with some form of infection due to a dermatophyte. In only one instance we observed a weakly positive reaction to the test. This is important, since the patients tested lived in New York and gave no history of a prolonged stay in the part of California where granuloma coccidioides is endemic. There is ample proof that the coccidioidin test is highly specific. The same conclusions may be drawn with respect to blastomycin and sporotrichin. With blastomycin, in contradistinction to coccidioidin and sporotrichin, negative reactions to the test may be encountered in the presence of the active disease. The histoplasmin test may be negative in a patient with active histoplasmosis. Positive reactions usually may be found in patients with the rapidly fatal type and also in patients who apparently have an abortive form. Occasionally cross-sensitization or false positive reactions may be noted for blastomycin and histoplasmin. Fishman stated that 60 per cent of several hundred patients with coc-

cidioidomycosis showed a positive skin reaction to histoplasmin. Katzenstein concluded that cross-sensitization occurred frequently with blastomycin.

4. CONJOINT SENSITIZATION TO PENICILLIN

Recent clinical and experimental studies suggest that penicillin, a derived product of the mold Penicillium, contains antigenic properties similar to those elaborated in superficial fungous disease. The local application of penicillin in patients with acute fungous disease may provoke a local exacerbation. Injection of the drug parenterally may result in the reactivation of a previous dermatophytid, produce in patients with present or previous active dermatophytosis a vesicular eruption of the hands and/or feet identical with the id reaction, or bring forth erythematovesicular lesions in areas of previous dermatophytosis.

Cross-sensitization experiments in the guinea-pig, utilizing both skin and uterus as test tissue, disclosed an intimate relationship between sensitization to penicillin and to T. gypseum infections. Whereas the nature of this relationship is still obscure, available evidence indicates that animal tissues with an induced sensitization to penicillin have likewise developed an allergic reactivity to trichophytin.

Clinical reactions to penicillin may be classified as (1) contact dermatitis; (2) sensitization of the vascular bed, resulting in urticaria, angioneurotic edema, serum sickness-like syndrome, erythematovesicular dermatitis, erythroderma id-like reactions and erythema nodosum (shocklike reactions are included in this group); (3) sensitization of other structures, e.g., asthma; (4) toxic effects, causing convulsions (especially after local cerebral application), peripheral neuritis and possibly agranulocytosis, and (5) indirect effects, precipitating an unrelated infection by destruction of antagonistic bacterial flora.

5. EXPERIMENTAL FUNGOUS INFECTION IN ANIMALS

This subject is considered partially in the first part of this chapter under The Trichophytin Test. It is further dealt with in Chapter XXVI. Not all fungi capable of being inoculated into laboratory animals cause a resultant "take." The dermatophytes, or fungi causing superficial infections in man, are about equally divided in regard to their capacity or lack of ability to infect laboratory animals. Bloch and his school did most of their work of establishing basic immunologic principles using a strain of A. quinckeanum. DeLamater and also Henrici used strains of T. gypseum as well as other species of fungi.

When a virulent strain of T. gypseum is inoculated cutaneously into guinea-pigs, the incubation period is four to six days, and the period of spread or development lasts seven to 10 days. A climax is reached by the twelfth to sixteenth day. The lesion then begins to disappear spontaneously, and healing is complete in 30 to 35 days. Considerable variations in the time factors occur when different species of fungi are used and even with different strains of the same species. The susceptibility, time for development of a reaction if the animal is susceptible and the appearance of the reaction are also variable when other laboratory animals such as kittens or rabbits are employed. When guinea-pigs and rabbits are subjected to additional inoculations, the incubation period is shortened and the reaction greater. Henrici found that intraperitoneal reinoculation of live spores or of trichophytin when the first infection had not quite healed resulted in a diffuse generalized reaction of the skin. If interested in experimental problems in which laboratory animals are to be used, the reader is referred to the original articles mentioned in the bibliography.

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CHAPTER VII

Nondermatologic Allergic Manifestations Due to Fungi

THERE is reason to believe that sensitization and immunity phenomena are of great importance not only in the development of the response of the patient with a fungous infection (symptoms and signs) but in the rate of response of the patient to most therapeutic measures. The subject of secondary allergic manifestations of the skin (dermatophytids) is discussed in Chapter IX in the sections on tinea capitis (pp. 58 ff.) and dermatophytosis (pp. 116 ff.); moniliids are discussed in the section on moniliasis (p. 150). It has been shown that specific sensitization to some genera of fungi occurs after infection, and this fact may be demonstrated by tests with fungus extracts. The possibility has also been considered that fungi may act as sensitizers without causing an actual infection. From this point of view we have investigated a number of cases of eczema of the hands in which the cause was obscure. Patch tests with trichophytin did not reveal any consistent sensitivity either on the affected area of skin or at a site remote from the eczema. We had the same negative results when we tested such patients with extracts of saprophytic air-borne fungi. From a theoretical standpoint, an immediate wheal and flare response to a suspected fungus allergin given by intracutaneous injections would speak in favor of a direct relationship.

1. ASTHMA

There have been investigations of other allergic diseases and their possible cause by the spores of air-borne fungi. Cooke found that house dust was a cause of asthma. The activity of the dust was diminished by heating. Van Leeuwen noted that in localities where patients with asthma were free of an attack there were few air-borne molds and yeasts. Cadham in

1924 reported three cases of asthma in which the disease was due to the spores of a wheat rust. He found positive reactions to an extract of the organism, and acute attacks resulted on the inhalation of a small quantity of the spores. Hansen found several species of Aspergillus and Penicillium to be excitants capable of producing a paroxysm. Hopkins, Benham and Kesten reported that in a case of asthma under their observation the attacks occurred in locations in which mold spores were abundant. There was cutaneous sensitivity to a strain of Alternaria present in the patient's home, and attacks were provoked by inhalation of the extract. Feinberg, Brown, and Conant, Wagner and Rackemann pointed out the importance of molds in the patient's environment as a cause of asthma. They performed many tests with the extracts of cultured air-borne fungi, and these resulted in a high percentage of positive reactions. Wagner and Rackemann noted that many patients with asthma obtained relief when kapok was removed from their immediate environment. Fresh kapok did not cause trouble; most of the reactions observed were produced by old material. They found that the principle in commercial kapok active in skin tests depends on the growth of molds in the kapok (vegetable) fibers. Wagner and Rackemann also found that steam sterilization of both cotton and kapok effectively changed the materials so that molds did not grow well on them. Rowe recently stated that all patients with possible bronchial asthma or allergic bronchitis should be tested with fungus extracts as well as with other allergens. Waldbott and Ascher consider sensitivity to rust and smut an important cause of seasonal allergy of the upper respiratory tract. In two cases they were able to reproduce asthmatic attacks by inhalation of rust. They consider the development of the attack during the rust and smut season and strong reactions to their antigens to be reliable features in diagnosis.

Further detailed and controlled work in this subject appears to be necessary in order to clarify the concepts. Few proved instances of true bronchial allergy to fungi have been reported.

2. HAY FEVER

Correlation between the incidence of attacks of hay fever and prevalence of air-borne fungi has been recorded. Difficulty may be experienced in ruling out air-borne pollens.

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CHAPTER VIII

Immune Bodies Circulating in the Blood

1. SUPERFICIAL FUNGOUS DISEASES

GREENBAUM investigated the Kolmer complement fixation test as applied to a group of serums obtained from patients suffering from a variety of superficial ringworm infections. The negative results indicated that the test is valueless and that few or no antibodies develop in the course of superficial ringworm. Precipitins were demonstrated in rabbit serums after infections with several different dermatophytes (Citron, Sharp, etc.). Kusunoki failed to demonstrate either precipitins or complement-fixing antibodies in experimental animals or in man infected with ringworm fungi.

As we have mentioned, Marcussen and others have demonstrated circulating antibodies, evidenced by passive transfer tests. In our observations this finding was obtained only in patients with infections due to T. purpureum. Per and Braude, Jessner, and Ayres and Anderson have demonstrated antibodies in patients exhibiting allergic rashes due to fungi. Ayres and Anderson showed that serum obtained from a patient with a trichophytid, if mixed with Sabouraud's agar in the proportion of 8 per cent, was completely fungistatic. Control tests which utilized serum of subjects free from infections or with infections localized to the feet showed no inhibition of fungi seeded on the medium. Traub achieved partial success with the therapeutic administration of serum obtained from patients who had been cured of trichophytid. Our unreported experiences have not entirely confirmed the reports of these investigators. When serums obtained from patients with trichophytid were added to dextrose agar, we noted partial inhibition, evidenced by a diminution in the diameter of the resultant growth. However, in a few instances retardation of the cultural

growth resulted when normal serum was added to the agar. We could not obtain complete fungistasis. Therapeutic use of serum in patients with fungous disease has been uniformly unsuccessful.

2. DEEP (INVASIVE) FUNGOUS DISEASES

Whereas in many of these deep fungous infections it is possible to demonstrate agglutinins, precipitins, opsonins and complement-fixing antibodies, such tests have not come into popular use, nor are they considered as reliable as other methods for diagnosis. This subject is considered further under the various individual diseases.

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CHAPTER IX

The Superficial Mycoses

IN THE majority of cases of fungous infection the eruption is confined to some part of the skin. There are two large groups of the mycoses: (1) ringworm, or tinea, in which the site of invasion and propagation of the fungus is keratin (stratum corneum, hair, nails) and in which, while dissemination by the blood stream may occur, the involvement of visceral organs is unknown, and (2) moniliasis, in which the yeastlike micro-organism is found in intertriginous areas but is also a common silent inhabitant of the gastrointestinal tract. Included also are tinea versicolor, erythrasma, myringomycosis, tinea imbricata and several other tropical mycoses and other fungous diseases which do not produce granulomas. Some workers subdivide the superficial mycoses into parasitic and saprophytic types, according to the degree of cellular reaction in the adjacent tissues. We do not share their point of view, since some of the more virulent (difficult to cure) infections caused by organisms such as T. purpureum or A. schoenleini show little reaction in the tissues, invoke little or no immunologic response and yet, therapeutically, are the opprobrium of dermatologists. To call these organisms saprophytes might be correct in the sense that they do not provoke reaction in the host, but this would be misleading from the aspect of response to treatment.

As a group, the superficial mycoses show a wide diversity of types and characteristics, and no generalization may be offered regarding their response to treatment. They constitute the bulk of fungous infections which plague the general population. The incidence of species varies in different parts of the world. We shall consider the various phases of the subject, including the clinical features and the treatment, under the respective titles. It is of interest, but so far of not much practical importance, that multiple fungous infections involving different species of dermatophytes are not uncommon. Muskatblit and we also have recorded a number of instances in which one infection antedates another, in which the different

species of fungi are working together or in which they are causing entirely independent infections.

In our discussion of ringworm we shall follow conventional lines, with some variations which seem indicated. We believe that the ideal approach is etiologic (according to Sabouraud), and we have tried to correlate this point of view with the time-honored division into clinical groups. It is our opinion that an exposition of the characteristics and habits of such a fungus as T. purpureum will be helpful, simplifying rather than confusing the subject. Dowding and Orr described three clinical types of T. gypseum; this seems to be another step in the right direction. Analysis of data compiled from the study of specimens from a particular locality is also valuable. Fowle and Georg reported on inflammatory infections in patients exposed to ringworm in cattle. They found that 14 of 25 cases of deep suppurative ringworm were caused by faviform Trichophyta.

We find it convenient to divide ringworm into five regional varieties, keeping in mind that a patient may have more than one variety at the same time. Table 12 indicates the predominant micro-organism of each.

TABLE 12.–Types of Ringworm Infection

Diagnosis	Organism
Tinea capitis	Microspora
Tinea barbae	Variable
Tinea glabrosa	Variable
Tinea cruris	E. cruris
Dermatophytosis (Onychomycosis)	T. gypseum and T. purpureum

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1. TINEA CAPITIS

(Ringworm of the Scalp, Including Favus)

Tinea capitis is a superficial fungous infection observed mainly in children before the age of puberty. In certain forms, the infection may persist into adult life, but it is unusual for the disease to appear then for the first time. The condition is characterized by loosening and partial loss of scalp hair in patches, breaking off of the infected hair, which loses its luster, and

inflammation varying in degree from fine, branny scaling in some cases to phlegmonous localizations in others.

(a) Etiology.—During the past few years, a widespread epidemic of scalp ringworm affected children throughout the United States. At this time (1948) there is some evidence that it is slowly resolving, but in many communities the problem is still acute. The predominant micro-organism is Microsporum audouini. Except under epidemic conditions, tinea of the scalp is usually due to one of two Microspora, M. audouini and M. lanosum. In New York under ordinary conditions the incidence of these micro-

TABLE 13.—Cause of Tinea Capitis As Found in New York City before and during the Epidemic

Organism	Nonepidemic Years 1935–38		Epidemic Years 1943–46	
	No. of Cases	%	No. of Cases	%
M. audouini	114	39.0	351	77.0
M. lanosum	115	39.4	79	17.3
T. violaceum	22	7.5	3	0.7
A. schoenleini	17	5.8	5	1.1
T. crateriforme	5	1.7	7	1.5
M. fulvum	3	1.0	6	1.3
T. gypseum	1	0.3		
T. sulfureum	1	0.3		
No growth or not diagnosed	14	4.8	5	1.1
Total	292	100	456	100

organisms is almost equal; they are the cause in about 80 per cent of all cases (Table 13). The remainder of the infections are caused by a scattering of micro-organisms (Table 13). In California and in most parts of the Western and Southern states, M. lanosum is the predominant organism. No definite statement, however, is possible without cultural studies. Lehman, in San Antonio, Texas, has observed that a greater percentage of infections were due to M. audouini, whereas Smith, in El Paso, reported that he rarely encountered this organism and that in most of his cases ringworm of the scalp was caused by M. lanosum. In the Midwestern and Eastern states, M. audouini probably is the most frequent cause of tinea capitis. In Europe, M. lanosum is uncommon; in most cases, ringworm of the scalp is caused by M. audouini. The condition is more often observed in cities than in the country and is seen chiefly among the poor, particularly when there is overcrowding. It affects more boys than girls, the ratio being about 3:1. Crocker stated that in 600 cases the disease was 6 per cent more prevalent in boys. Beeson noted that 85 per cent of his patients were boys. In Pardo-Castello's series, there was only one girl to 31 boys. However,

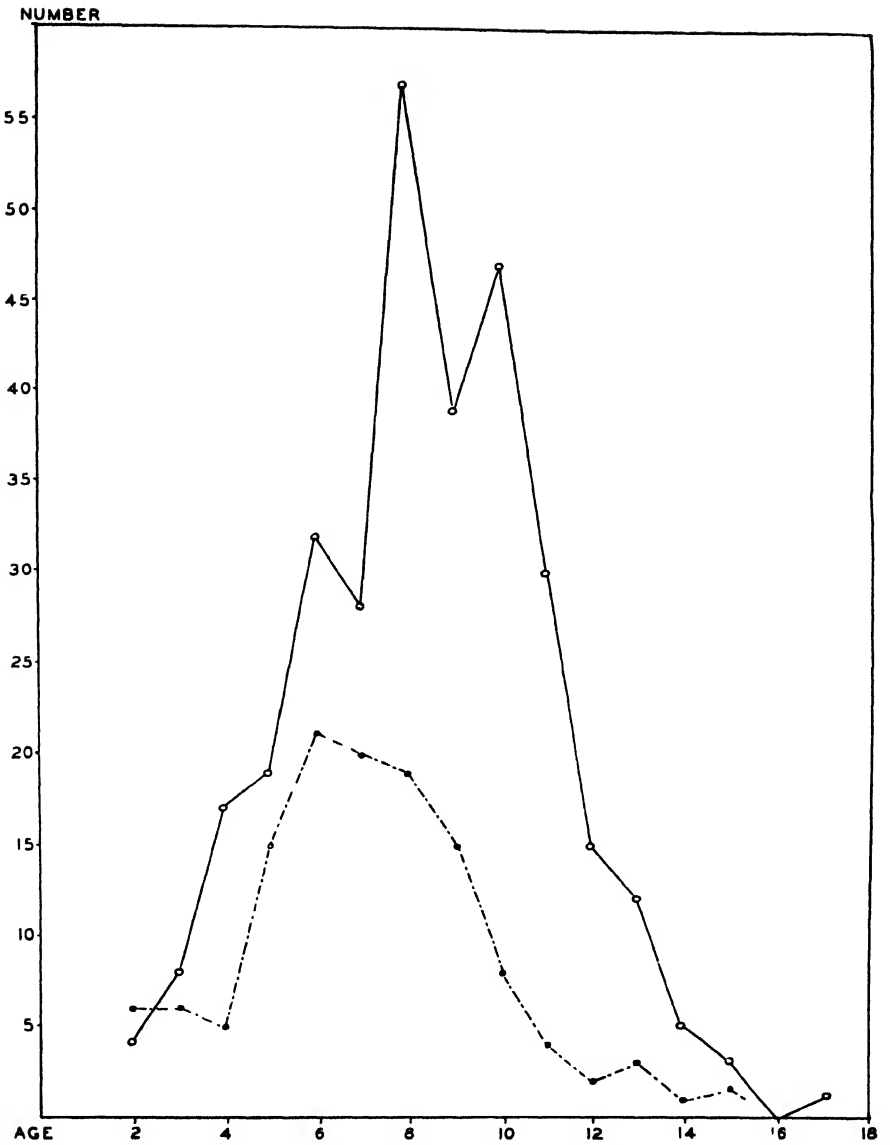

FIG. 5. Age incidence of 444 children with tinea capitis due to Microsporum audouini. Solid line represents 317 white children; broken line, 127 Negro children.

Fox and Fowlkes found that in 48 recorded instances of ringworm of the adult scalp, 32 women were affected (66 per cent). In our experience the highest peak of infection is reached at age 8. The disease may occur in epidemics in schools, orphan asylums or camps or wherever a number of children congregate; it is spread by direct contact with an infected person, with an infected comb, barber clippers, plush (movie) seat, hat or other article or,

TABLE 14.—Incidence of Species of Fungus Causing Nonepidemic Tinea Capitis in the United States and Canada

Authority	Location	No. of Cases	M. Audouini, %	M. Lanosum, %	Other Species, %
White	Boston				
Corlett	Cleveland	M. audouini stated to be the predominant organism			
Wende	Buffalo				
Beeson	Chicago				
Greenwood	Boston	40	25.0	67.5	7.5
Burgess	Montreal	62	32.2	33.9	33.9
Pardo-Castello	Havana	32	...	100.0	...
Davidson and Gregory	Winnipeg	75	57.0	43.0	...
Cleveland	Vancouver	100	...	100.0	...
Mook	St. Louis	In majority of cases acquired from animals			
Weidman	Philadelphia	36	41.7	50.0	8.3
Anderson	Los Angeles	..	...	Most frequent	...
Smith	El Paso	..	Rarely found	...	...
Binkley	Cleveland	..	70.0	30.0	...

in case of certain types of infection, with kittens or other pets. It is interesting that with animals, as with human beings, only the young are susceptible to the infection. The chief danger, then, of dissemination of the infection from animals lies in young pets of unknown origin, particularly kittens. Race does not appear important except that with favus most patients are either native-born Russian, Polish or Italian or descendants of immigrants from these countries.

(b) Types of infection.—The infecting micro-organism first invades the stratum corneum, later enters the hair follicle and finally attacks either the superficial or the deep parts of the hair. The cardinal symptoms of tinea of the scalp are partial loss of hair in patches, breaking off and lack of luster of the infected hair and varying degrees of inflammation. Atrophy and scarring may follow certain types of infection.

In most textbooks a separate section is devoted to kerion. We do not

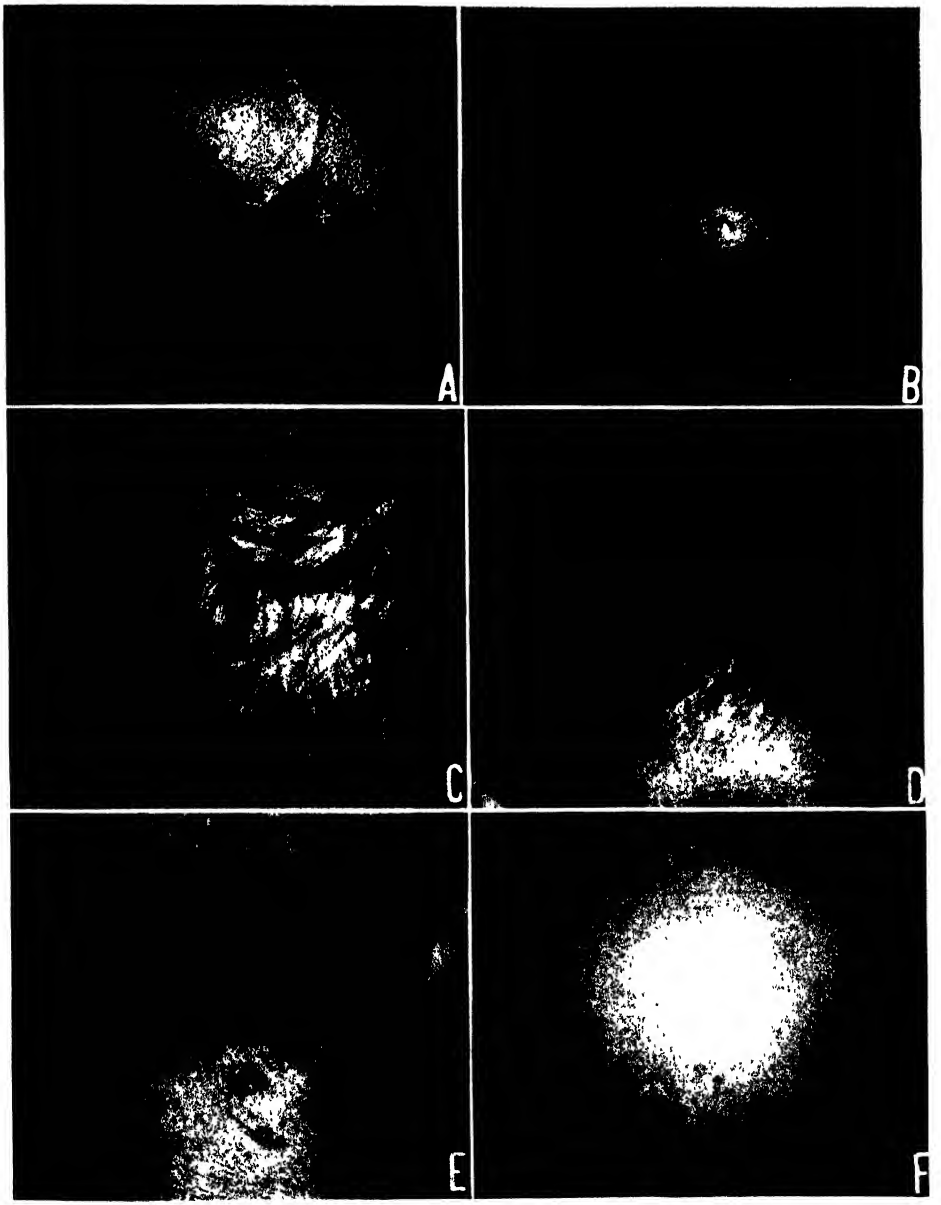

FIG. 6. Tinea capitis due to M. audouini. *A*, scattered scaly patches of pseudo-alopecia containing hair stumps in a boy aged 7. *B*, the same patient, showing extension of infection to the smooth skin of the forehead. *C*, regrowth of hair has masked the disease. *D*, luminogram of the patient shown in *C*, revealing infected hairs. Examination of patients under filtered ultraviolet rays often brings to light hidden foci not detectable during the ordinary clinical examination. *E*, pustular ringworm of the type more commonly caused by M. lanosum. *F*, complete epilation of scalp hair following roentgen treatment. This is the therapy of choice in most instances of tinea capitis caused by M. audouini.

consider kerion to be more than a marked tissue reaction to the infecting micro-organism: at the top of the list, so to speak, with simple scaling at the bottom. Kerion is a painful, elevated, boggy, erythematous, localized tumefaction due to one of several species of fungi. We have records of kerion due to M. lanosum, M. audouini, Microsporum fulvum, Trichophyton crateriforme, T. gypseum and Trichophyton niveum. In the main, the characteristics of kerion are the same, irrespective of the causal fungus, and in most instances cure of the fungous infection follows the disappearance of the kerion.

In another particular we deviate from the customary teaching. We cannot see any logic in the traditional respect paid to favus when it is considered more than a type of tinea capitis. The clinical findings of favus are frequently characteristic, so the retention of the name is useful.

Since the clinical findings and the course of the disease vary a great deal, according to the infecting micro-organism, we shall discuss tinea capitis further under the headings of the causative fungi as follows:

(*1*) *Microsporum audouini.*—This fungus is responsible for the classic type of scalp ringworm known as the "gray patch"; it is the common cause of epidemics in orphanages and other institutions. The onset is usually insidious, and the duration of the infection averages over eight months. When the condition is first detected by the parent, guardian or teacher, there are several small areas in which the hair is dull and broken off. The surface of the patch is usually scaly. As a rule little redness is noted, but occasionally a considerable degree of inflammation may be present. We have observed that the infection frequently begins along the part of the hair or where the hair is short. When first examined, the lesions are usually in the occipital and temporal regions. Usually a number of lesions spread peripherally, finally becoming as large as a silver dollar or larger. There is not much tendency for the infection to spread to other parts of the body. In the cases observed in New York during an epidemic (1943 to 1947) there was a tendency for the infection to localize to the occipital region. The lesions were more frequently inflammatory than in the ordinary sporadic disease, and associated lesions on the glabrous skin were more commonly observed than in the sporadic cases. Montgomery and Walzer reported a case of infection of the eyelashes in a patient with tinea capitis.

(*2*) *Microsporum lanosum.*—There may or may not be a history of contact with a stray or newly acquired kitten or other young animal. Various home and proprietary remedies have usually increased the inflammation. In other members of the family, particularly the mother or other children, lesions may develop on the glabrous skin. The infection tends to show considerable inflammatory reaction. The first patch to develop is frequently

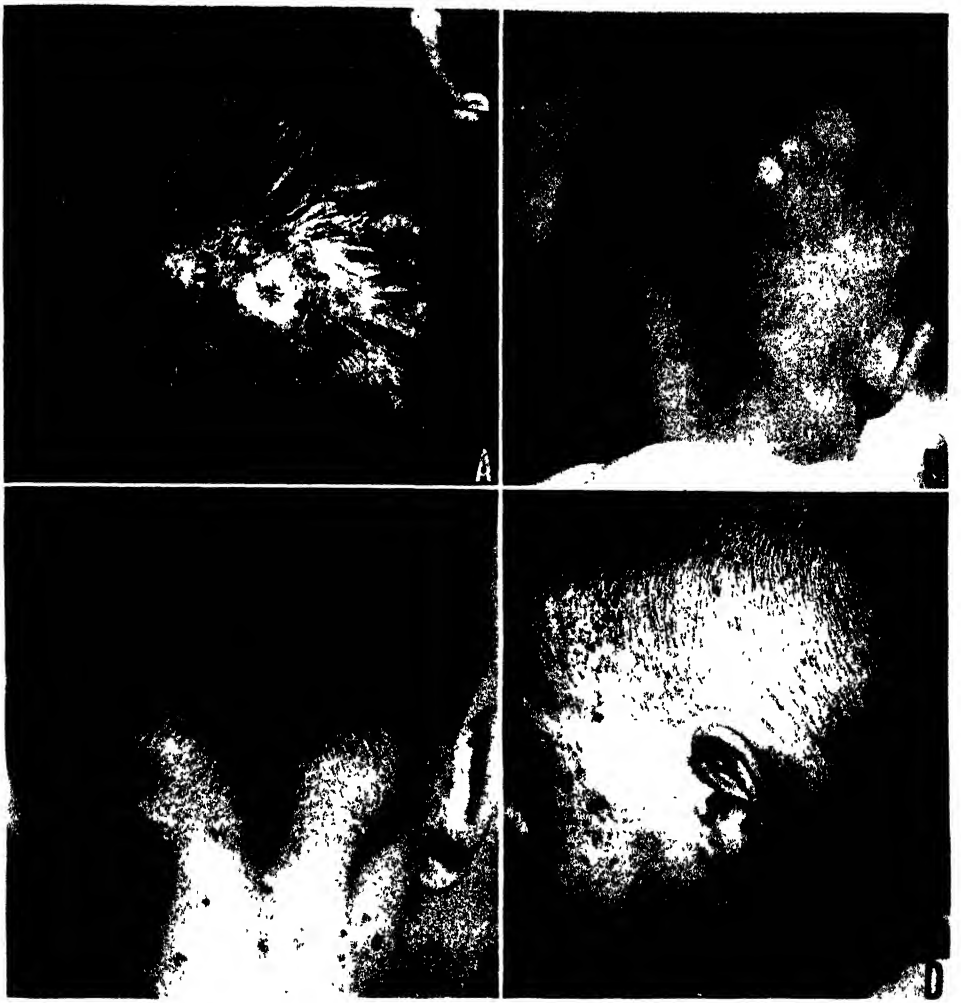

FIG. 7. Tinea capitis caused by M. lanosum. *A*, typical acute inflammatory involvement with follicular pustules. *B*, areas of complete alopecia due to the severe follicular inflammation. In such cases spontaneous cure results. *C*, extension of the infection below the hair line, an occurrence not uncommon in this type of infection. *D*, extension of the infection to the glabrous skin of the face.

the largest; secondary lesions are usually smaller. The duration is usually short (under three months). There is noticeable loss of hair in the affected patches with slight or, more commonly, marked inflammation and tenderness. Broken-off hairs may be found at the periphery of a lesion.

(3) *Microsporum fulvum.*—An infection due to this fungus may or may not be acquired from an animal. The duration is usually short (one month or less). There is a tendency for the infection to remain localized to only one part of the scalp. Inflammation is usually marked, and kerion is not unusual. In our experience there is always noticeable edema of the affected tissues.

(4) *Trichophyton violaceum.*—In this type of ringworm of the scalp, small scattered patches develop insidiously. The duration of the infection is frequently many months or even years. The disease may not be cured at puberty. The fungus invades the cortex of the hair (endothrix infection), and the hairs break off close to the scalp. The appearance of the infected scalp has led to the name "black dot" ringworm. In many instances, the hairs break off just below the surface of the scalp, which results in a minute secondary pyogenic infection with subsequent crusting, not unlike that due to ingrowing hairs of the beard. We have never found T. violaceum in the pus in these lesions, although we have tried innumerable times. After many months there is usually some atrophy or scarring.

(5) *Trichophyton crateriforme.*—The clinical appearance and course of tinea due to this organism differ materially from those of infection due to T. violaceum, since the infection may appear in one or more patches and the infected hairs usually do not break off at the surface of the scalp; rarely the clinical appearance is that of "black dot" ringworm. In addition there is usually secondary infection; crusting and kerion are seen in three of five cases. As in kerion due to other fungi, the infected hairs are shed because of the inflammatory process, and cure may be spontaneous. The organism invades the cortex of the hair (endothrix infection) and is not transmissible to laboratory animals. Infection with T. crateriforme may be of several weeks' duration when first observed.

(6) *Trichophyton sulfureum.*—The only scalp which we observed to be infected with this fungus presented a diffuse reddened scaly rash over the occiput. Throughout this area were numerous small stumps, interspersed with normal hair.

(7) *Achorion* (*Trichophyton*) *schoenleini.*—This micro-organism (essentially an endothrix Trichophyton) is the cause of an infection designated as favus. The clinical manifestations are usually characteristic. The usual focus is the scalp, from which the disorder may spread to the nails or to the glabrous skin. At first there is a small spot of scaly inflammation. Around

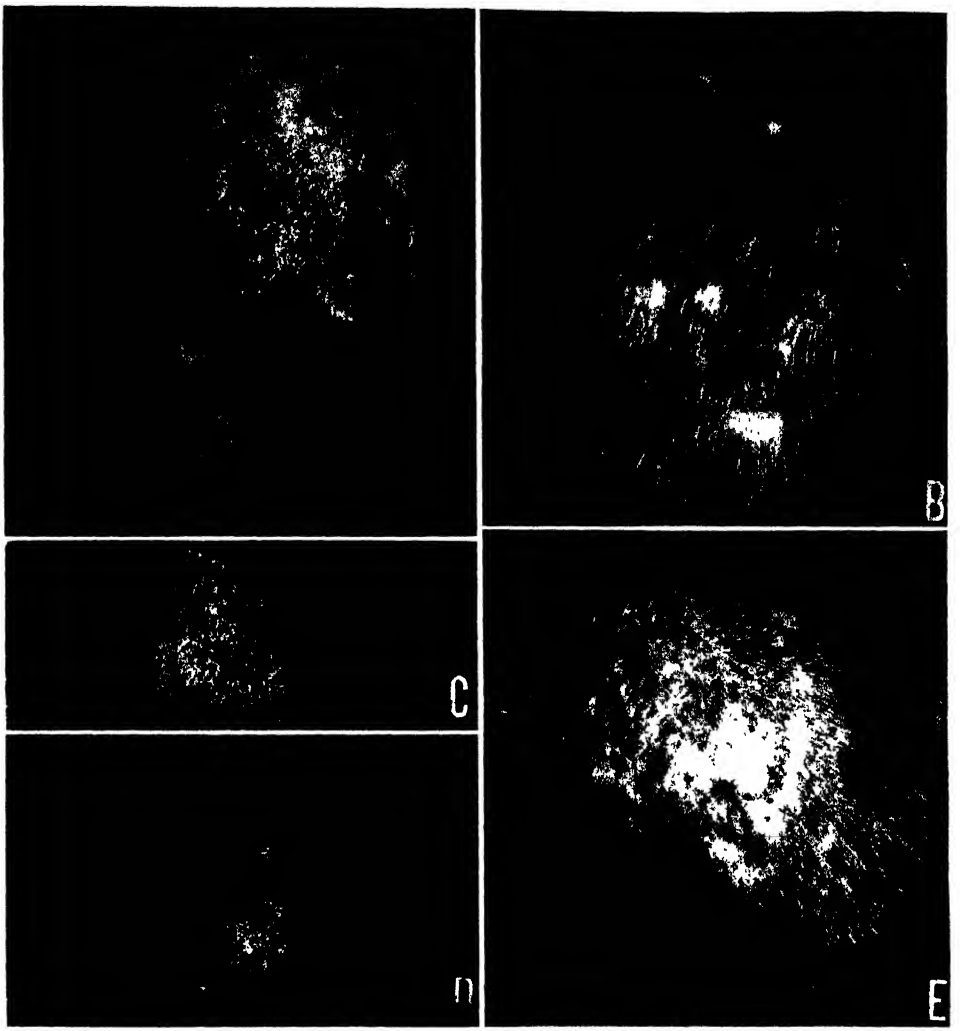

FIG. 8. Tinea capitis due to endothrix Trichophyta. *A*, severe inflammation producing boggy infiltrations caused by T. crateriforme. *B*, the subject shown in *A*, after cure by simple topical measures. There was eventually a complete regrowth of hair in the areas of alopecia. *C*, *D* and *E*, examples of "black dot" ringworm, caused by T. violaceum. In *E* the hair has been cut in a patch around the infected site. The black dot is caused by breaking off of the hair near the surface. Small pyogenic superinfections are common. Tinea capitis due to T. violaceum is the most difficult type of all to cure.

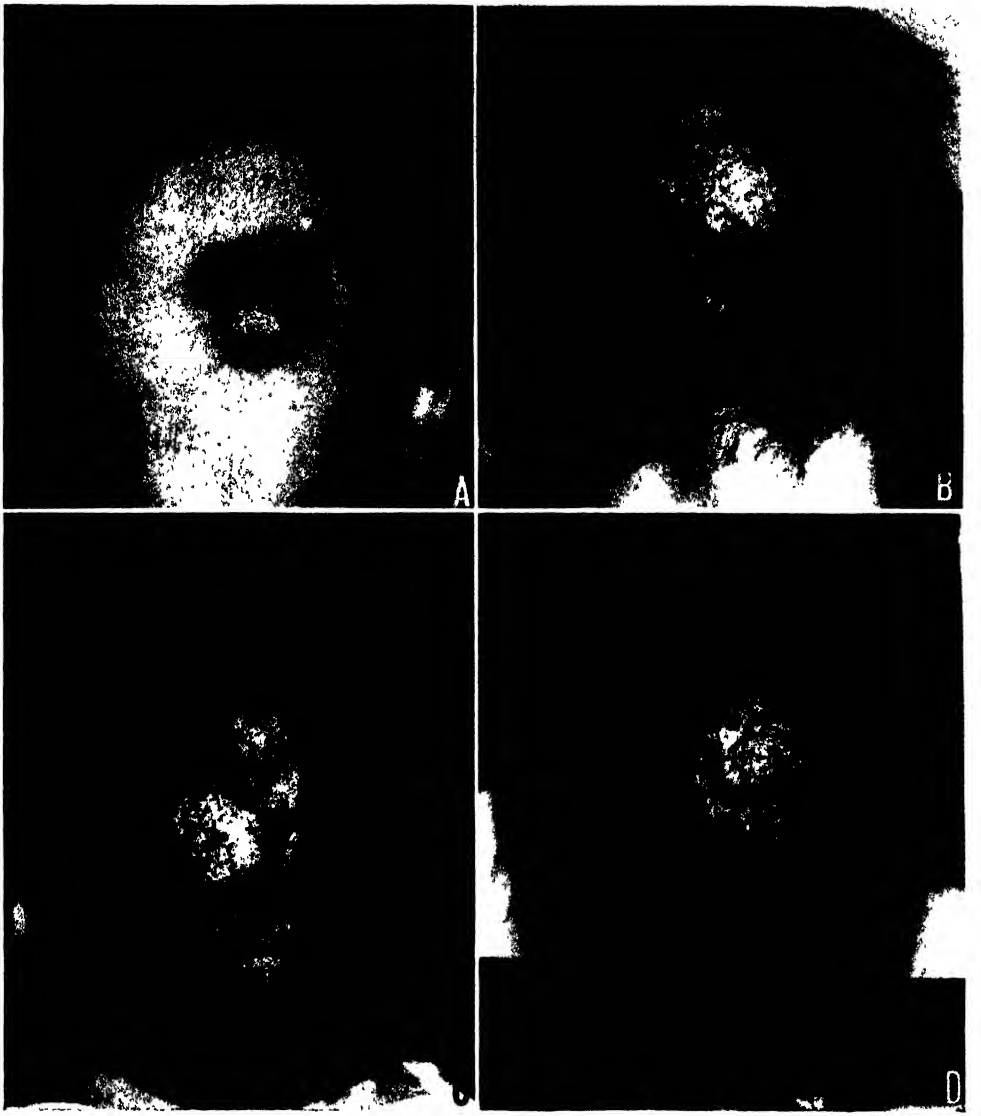

FIG. 9. Kerion, which may be due to any one of many species of fungi. Four instances of kerion are shown, each caused by a different fungus. *A*, M. fulvum. *B*, T. crateriforme. *C*, M. lanosum. *D*, M. audouini.

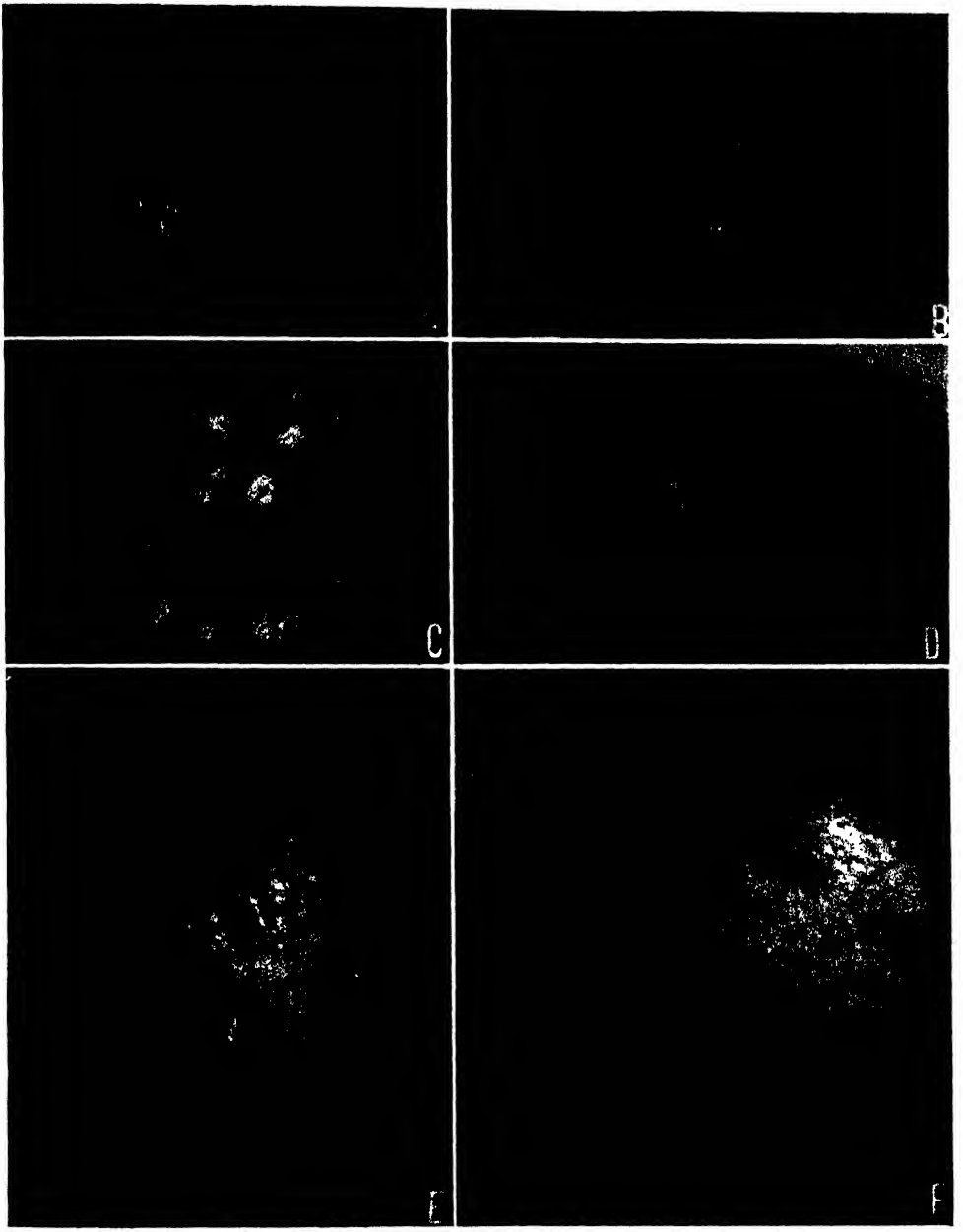

FIG. 10. Favus of the scalp. *A*, early single patch with crusts but no alopecia. Regrowth of hair occurred, and there was no resultant atrophy. *B*, untreated involvement of short duration, showing thick crusts but no demonstrable atrophy. *C*, multiple foci of infection with crusting. The areas of alopecia are the result of manual epilation. Complete regrowth of hair occurred without atrophic changes of the scalp. *D*, scutula with small atrophic areas; the process was of 15 years' duration. *E*, condition of long duration, showing an atrophic patch with active spreading infection. *F*, result of neglected infection, with atrophy of the scalp and permanent alopecia.

the hair follicles may be noticed yellow points which are soon observed to be crusts. These yellow crusts increase in size and finally become cup-shaped, when they are known as scutula. The convex side of the scutulum presses down on the skin; the concave side faces outward. They are sulfur colored, friable and pierced with hair. A distinctive mousy odor may be readily detected. The infected hair is brittle and lusterless, but not necessarily fractured, certainly not as extensively as with infections due to Microsporum. Owing to pressure of the scutula the hair in the affected sites loosens and falls out and may not return. The skin in the affected patches is atrophic. When untreated, the disease spreads slowly to cover a large part of the scalp. After several years there may be spontaneous cure, but permanent alopecia in patches is the final result.

In another manifestation of favus on the scalp there may be a diffuse superficial but adherent scaling, with little, if any, alopecia or evidence of follicular involvement. The resemblance to seborrheic eczema may be striking. Since most of our patients have been adults, it is our impression that this form is more apt to appear after puberty, when there is more resistance to follicular infections of the scalp. It is well to keep in mind the possibility of favus when a scaly condition of the scalp refuses to respond to the remedies commonly employed in the treatment of seborrheic eczema. Whittle reviewed the clinical features of cases presented in Great Britain during the past few years. He concluded that atypical and minimal manifestations, with scutula rarely present, may lead to an error in diagnosis.

(8) *Trichophyton gypseum.*—While rare in New York, instances of infection with this micro-organism are observed more commonly in other parts of the country, particularly in the Middle West. The chief characteristic is a violent inflammatory reaction, ordinarily with the development of kerion. There is usually a history of contact with an infected animal. Familial infections may occur, in which case each member may have a particular manifestation unlike the others. In a family which came under our observation a boy had a widespread infection simulating psoriasis and involving, among other areas, the hands, feet and face; another child had kerion and a third child tinea glabrosa of an eczematous type (Fig. 13).

(c) DERMATOPHYTID (MICROSPORID, TRICHOPHYTID).—Jadassohn, in 1911, before the Swiss Medical Congress, first described an eruption in patients with kerion which consisted of small, follicular elevations, occurring either in groups or diffusely, in large or small numbers, and which disappeared spontaneously. There was a resemblance to lichen scrofulosorum, but the histologic picture was different, and a patient's skin did not react after the injection of tuberculin. There was a symmetrical distribution; the trunk was the usual site, and often the extremities were involved as well. In some

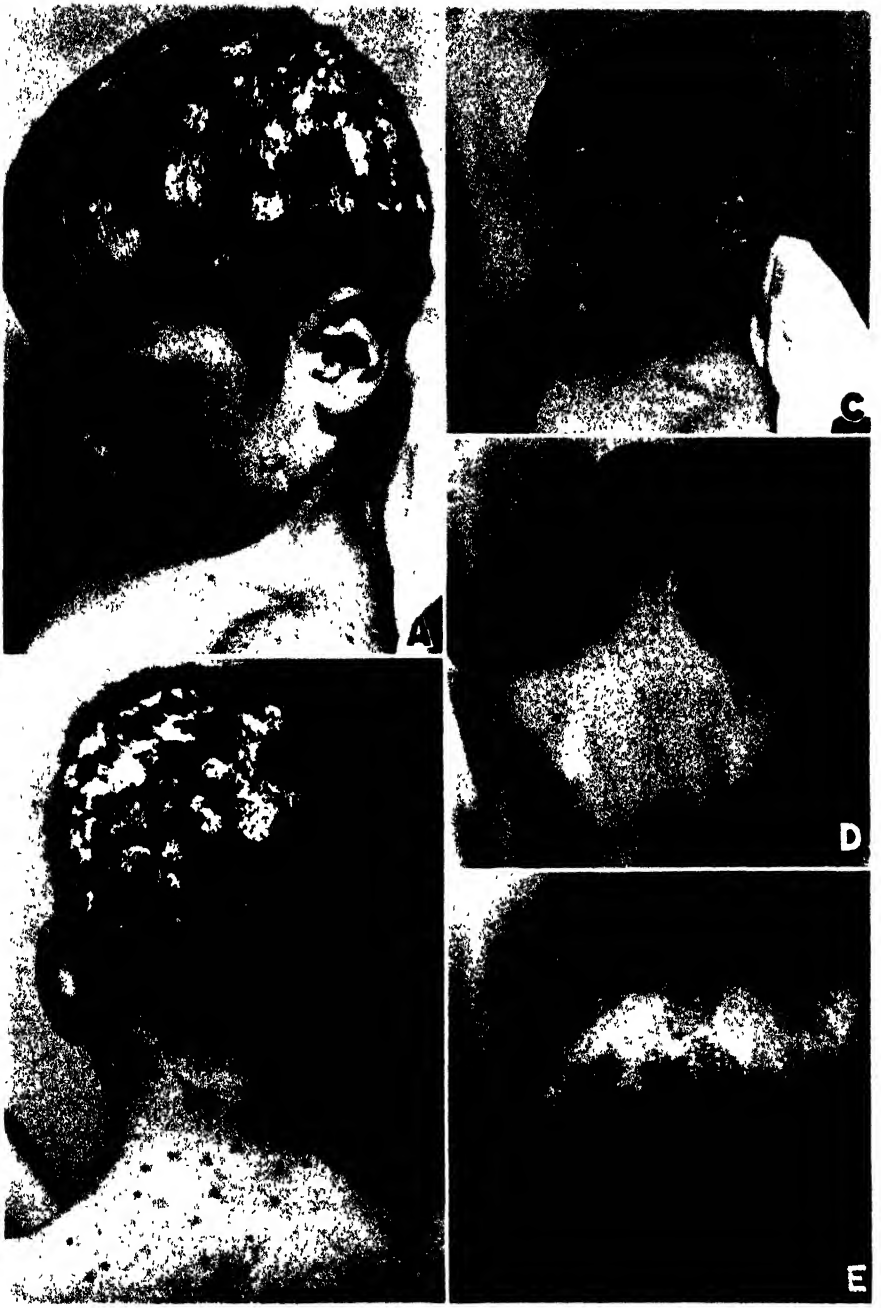

FIG. 11. Favus in a boy aged 6. Other members of the family were also affected. *A* and *B*, typical neglected crusted lesions (scutula). *C* and *D*, following daily use of soap and water and application of salicylic and sulfur ointment for one week, the crusts have disappeared. *E*, epilated scalp, showing residual erythema at sites of former lesions.

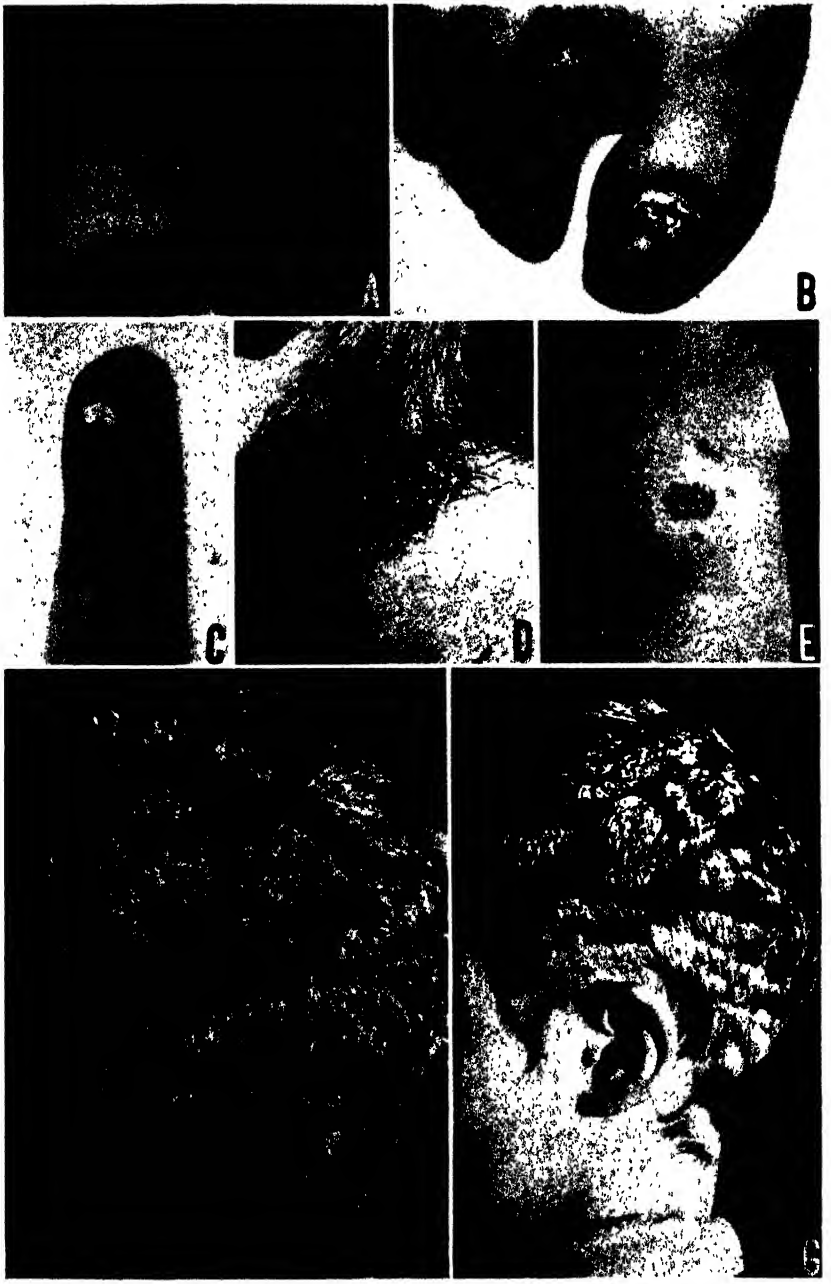

FIG. 12. Favus. *A*, ill-defined scaly lesion above the eyebrow. *B*, onychomycosis of one toenail. *C*, onychomycosis of a fingernail. *D* and *E*, scutula on the smooth skin. *F* and *G*, extensive involvement of the scalps of two patients; in both cases the disease had been unrecognized and untreated. When lesions are present on the smooth skin or the nails are affected, the scalp is usually concomitantly involved.

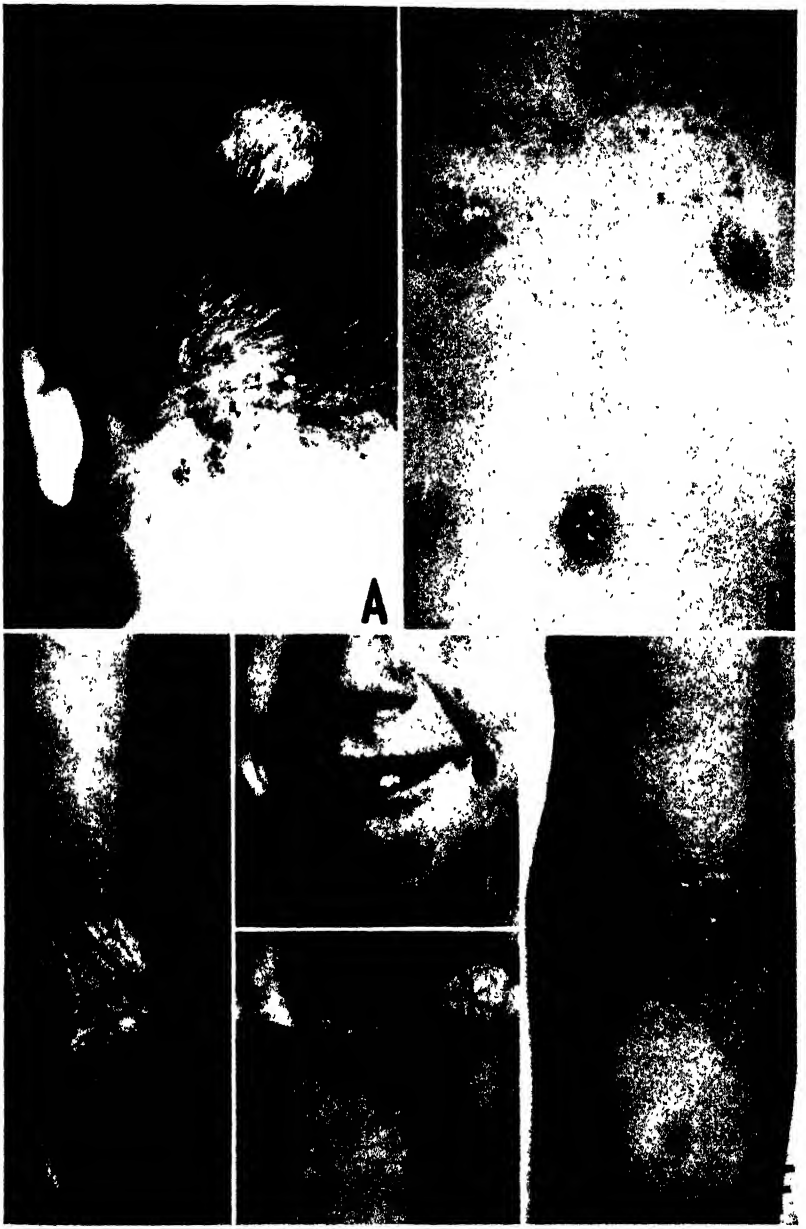

FIG. 13. Ringworm infection of three members of a family, showing variations in the site of involvement and in the degree of inflammation. The source of the infection was not determined. All three patients responded readily to fungicidal therapy. The culture in each case revealed T. gypseum (granular). *A*, pustular tinea capitis of one month's duration in a boy aged 5. *B*, tinea glabrosa (eczematous type) of two weeks' duration in a girl aged 4. *C*, *D*, *E* and *F*, involvement of the right hand and forearm, face, toes and right elbow, of one year's duration in a boy aged 8; in all sites the lesions showed mild inflammation.

instances horny spikes, or spines, capped the lesions, when the appearance was similar to that of lichen spinulosus. The work of Jadassohn, Bloch, Guth and others of their school soon showed that these rashes (and others resembling erythema toxicum, erythema multiforme or the like) were expressions of cutaneous allergy due to a hematogenous spread from an inflammatory focus on the scalp. We designate a rash of this character as dermatophytid. Fungi or their products caused sensitization of the skin, and this altered reaction resulted in lesions which in themselves were sterile. We have observed a number of instances of dermatophytid in children with tinea capitis in which the appearance of the rash coincided with or followed a depilating dose of roentgen rays. We studied a rash on a child who received trichophytin therapeutically. In all instances the patient exhibited a strong reaction to the intracutaneous test with trichophytin. The origin of the rash was always an inflammatory lesion or lesions, most frequently being frank kerion. Sometimes strong topical applications causing marked inflammatory changes have resulted in dermatophytid.

The subject is further discussed in the section on dermatophytosis, pp. 116 ff.

(d) Reaction to trichophytin.—Patients with ringworm of the scalp vary in their reaction to trichophytin, mainly in accordance with the type of infecting micro-organism. There is usually more response when the fungus is also pathogenic to animals. The reaction may be valuable in helping the physician to determine the type of therapy. In infections due to M. audouini the response to the intracutaneous test with trichophytin is usually slight. With endothrix infections, such as those due to A. schoenleini and T. violaceum, the reaction to the test is commonly negative or only slightly positive. When tinea of the scalp is caused by M. lanosum, M. fulvum, T. crateriforme or T. gypseum, a moderate or marked reaction to trichophytin is the rule.

(e) Filtered ultraviolet rays.—The nature and use of these rays has been mentioned elsewhere. Since under the rays a suspected scalp will show a characteristic fluorescent effect whenever infected hair is present (except in the rare instances of ectothrix infection), it is apparent that the use of ultraviolet rays is important in revealing not only the presence but the extent of the infection. One is frequently surprised to find widespread involvement when clinical inspection has led one to believe that only one or two areas of infection were present. Furthermore, we have observed several patients in whom regrowth of hair in patches of partial alopecia due to a tinea infection was sufficiently vigorous to mask the disease. Numerous infected hairs were observed by the test of fluorescence.

Hairs infected with one of the commonly found Microspora (M. lanosum,

M. audouini or M. fulvum) are all revealed as bright green stubs under the rays. In the very early stage of infection the color may be noted only in the portion of the infected hair nearest the scalp. No fluorescence will be revealed in infections due to M. ferrugineum. Hairs infected with A. schoenleini vary from lighter green to dull gray; when T. violaceum, T. crateriforme or T. sulfureum is the infecting micro-organism the hair is dull gray and yet to be differentiated from normal hair. Light brown or gray hair fluoresces somewhat. This might lead to confusion as also might the fluorescence due to petrolatum or to some drugs.

We believe use of filtered ultraviolet rays to be of the utmost importance in the diagnosis and management of tinea of the scalp. Their use to determine when cure has taken place is indispensable; if the patient is being treated by topical applications, progress may be noted under the rays. Cleveland raised the question whether a child might show fluorescence but be noninfectious when the disease was asymptomatic. He found that such is not the case, being able to reproduce the disease from such cases in animals. He points out the danger to others when children who are clinically cured and yet have infected hairs, as revealed by the fluorescence test, are not treated or whose treatment is lapsed. This method of examination, however, should not entirely supersede the older procedures. It is important to observe fungous elements under the microscope, and it is desirable to culture the causative micro-organism.

(f) DIFFERENTIAL DIAGNOSIS.—It is taught at the Cornell University Medical School that patchy loss of hair from a child's scalp denotes ringworm until repeated laboratory investigation has failed to substantiate the diagnosis. When there is little inflammatory reaction, alopecia areata may be simulated. In alopecia areata, however, there is a sudden complete loss of hair with no scaling on the surface of the patch. Trichotillomania and trichokyptomania have proved puzzling to us in a few instances, but in such cases the child is usually neurotic, the apparent or actual loss of hair is near the front of the scalp, and again there is no scaling.

Seborrheic dermatitis may be differentiated by the presence of greasy scales and the absence of patchy loss of hair. The superficial form of favus may so closely resemble seborrheic dermatitis that only the lack of response to therapeutic agents may favor the diagnosis of favus.

When marked inflammation is present, pyoderma is the chief condition to differentiate. Pyodermic lesions on the scalp of a child usually spell pediculosis, and an inspection of the scalp ordinarily reveals nits. Pustular lesions, however, may appear secondarily to a focus of infection such as a discharging ear. We have observed an instance of pustular lesions of the scalp due to the ingestion of iodized salt.

Tinea amiantacea (asbestos-like tinea) was first described by Alibert in 1832. The disease has lately been reviewed by Becker and Muir. It should probably be classed as a pseudomycosis, since no constant fungous flora is demonstrated. It is important, since the clinical signs simulate those of tinea capitis. It is thought by some to be a form of seborrheic eczema and by others to be an aberrant form of psoriasis. The disease is manifested on the scalp by a binding together of the proximal portions of the hairs by asbestos-like laminated scales. It may be localized to one area or distributed over the entire scalp. Scaling is present on the involved surfaces, but usually with little visible inflammation. The disease is said to occur most frequently in children. There is no tendency to loss of hair, nor is the structure of the hair altered. The peculiar large yeastlike bodies which have been noted are probably artefacts caused by the action of potassium hydroxide on grease. The condition is usually helped by frequent washing of the scalp and by the application of a salve containing sulfur or tar. Recurrence is common.

Trichorrhexis nodosa is a disease in which the hairs show one or more nodular enlargements. Microscopically, these nodules are due to partial transverse fracture. When the fracture is complete, the end is frayed. A certain amount of thinning of the hair may result.

Monilethrix, a congenital disease, also produces a variable degree of alopecia. The affected hairs have a peculiar undulated appearance due to regular variations in their diameter. Where the diameter is reduced, a fracture is apt to occur. Keratosis pilaris is often associated, and generalized scaling of the scalp is common.

In all cases of suspected infection, one is not justified in being content with a clinical diagnosis. Examination of the scalp under filtered ultraviolet rays and microscopic examination of material such as hair and scales are mandatory. It is also highly desirable to inoculate a culture medium and determine the specific diagnosis. Such procedures are simple to perform and yield exact information.

(g) Prognosis.—There is a marked difference in the prognosis with different types of ringworm of the scalp. In general, infections caused by fungi which are also pathogenic to animals are quickly cured, and often cure is spontaneous. The causative fungi not pathogenic to animals cause infections which are resistant to treatment and which, if unchecked, remain for an indefinite period. Microspora in general are responsible for benign infections; Trichophyta produce either infections rebellious to treatment (endothrix) or severe inflammations (ectothrix). The infections due to Microspora tend to clear up spontaneously at or about the age of puberty. Rothman and his co-workers have demonstrated that this spon-

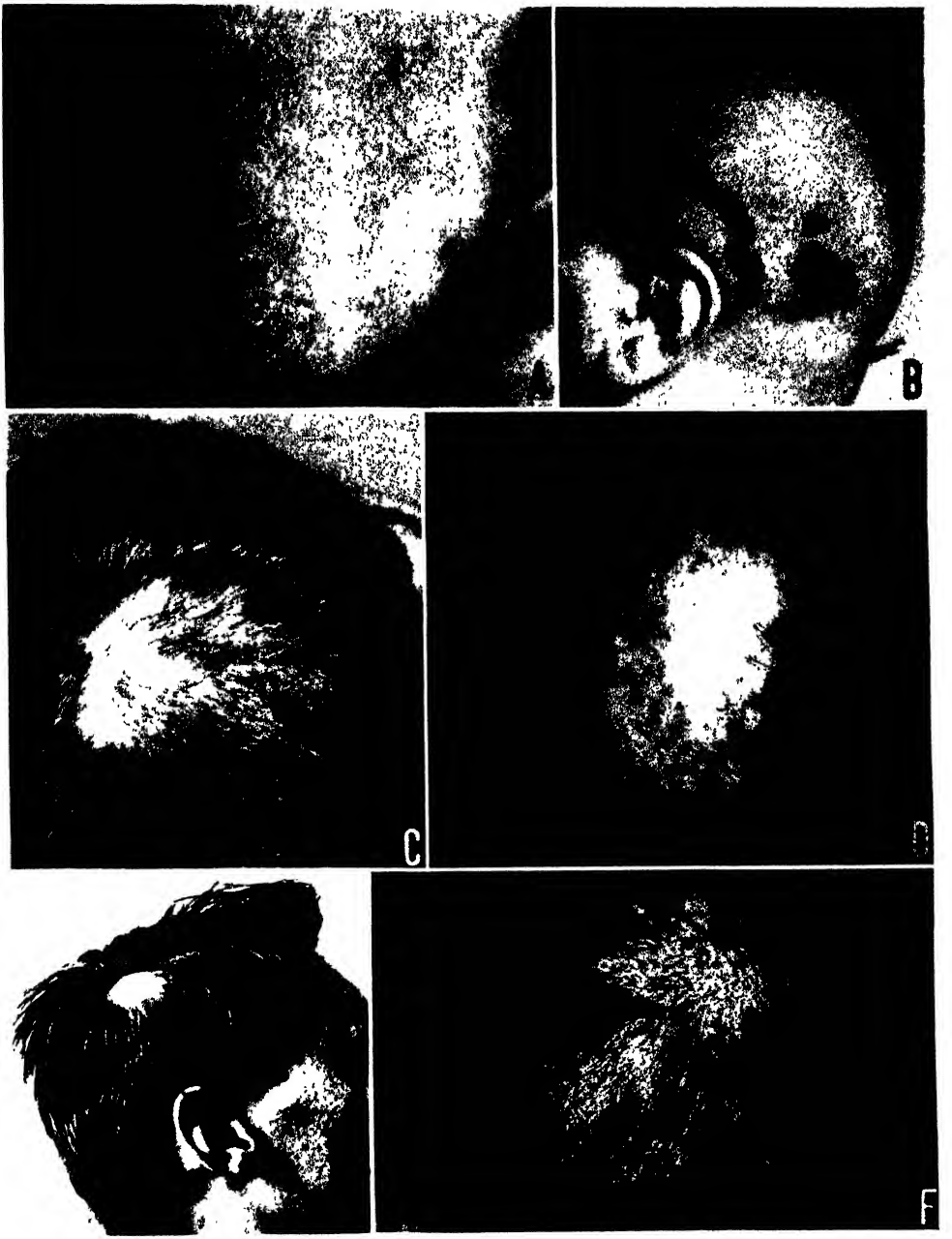

FIG. 14. Diseases often confused with tinea capitis. *A*, seborrheic dermatitis. *B*, psoriasis. *C*, trichotillomania. *D*, folliculitis decalvans. *E*, alopecia areata. *F*, trichorrhexis nodosa.

taneous cure of M. audouini infections (and also the immunity of adult scalps) is due to the secretion, at puberty and later, of sebum which contains, in higher concentration than before, low-boiling saturated fatty acids with selective fungistatic and fungicidal effect on this fungus. We believe that an entirely different mechanism of cure (hypersensitivity; inflammation; epilation of hair) is responsible for the cure of M. lanosum infections and for those due to other fungi capable of sensitizing the skin. Favus and the manifestations of the endothrix organisms persist for an indefinite period unless treated. We have seen instances of infection with A. schoenleini which lasted over 20 years. It seems that eventually even here the fire burns out, but cinders (in the form of atrophy) may be noted. The most resistant conditions which we have treated were caused by T. violaceum (an endothrix).

In our experience, 90 per cent of patients with M. audouini infections may be cured in nine weeks if roentgen epilation is undertaken.

(h) TREATMENT OF NONRESISTANT INFECTIONS.—In several publications we have called attention to the tendency to spontaneous cure and to the success of local measures alone when tinea capitis is caused by M. lanosum. The series of patients reported cured by Poth and Kaliski following therapy with estrogens were not controlled by filtered ultraviolet ray studies, nor were cultures done. The estrogens were rubbed on the scalp in most cases, probably assisting cure by rubbing out the infected hairs. Unless there are special reasons, one may not wish to subject a child with this type of ringworm to epilation of the entire scalp by means of thallium acetate or roentgen rays or to the administration of estrogens. This also applies to infections due to an ectothrix Trichophyton, to markedly inflammatory conditions (at least until the process is less severe) and to states of vigorous reaction to trichophytin, irrespective of the cultural diagnosis. In all such cases the treatment should be conservative. We use one of several topical applications, such as an ointment containing 5 per cent ammoniated mercury or one containing 1 per cent thymol, 0.5 per cent oil of cinnamon and 0.5 per cent iodine crystals. Salves containing any antiseptic in a not too concentrated form would probably be of equal benefit.

We have previously pointed out that cure of these infections invariably occurs because the infected hair comes out and not because of any direct fungicidal action of an applied medicament. Because of this the salve should be mildly stimulating, to assist in loosening the hair but not strong enough to cause too much inflammation, and fungicidal, to prevent the spread of the infection. Besides the drugs just mentioned, sulfur in an ointment base (5 to 10 per cent) and iodine crystals (10 per cent) in wool fat will be found equally effective. We advise against the use of salicylic

acid, chrysarobin, croton oil, oil of turpentine and the like as unnecessarily hazardous. The loosened hair is best removed by frequent shampoos. The use of a mild soap applied with a brush has been found effective. If the shampoo is carried out too vigorously or too frequently, the infected hair may be kept rubbed off close to the scalp instead of being epilated. The result is that the infection does not respond as rapidly as expected. The remedy is to lengthen the interval between shampoos and to use less vigor in applying the hand brush.

(i) TREATMENT OF RESISTANT INFECTIONS.—When the infecting microorganism is M. audouini, A. schoenleini or one of the endothrix Trichophyta (chiefly T. violaceum), unless there is a vigorous response to the test with trichophytin, some type of depilating treatment is usually required. Livingood and Pillsbury have shown that even M. audouini infections will often become spontaneously cured if left long enough. In practice it is not considered wise to defer active treatment. There are three methods which may be used: (1) manual epilation with salves and adhesive plaster, (2) roentgen epilation and (3) epilation by the thallium salts. If the infection is due to M. audouini and the patient is near the age of puberty, expectant treatment rather than depilating measures may be undertaken. We have attempted to cure the resistant infections by means of vaccinotherapy (trichophytin), substitution of another fungus capable of producing an inflammatory response in the scalp, short wave ultraviolet radiation and other modalities and methods without any consistent effects. The poor results which we obtained from the therapeutic use of trichophytin were similar to those reported by other observers who studied their cases from the etiologic point of view. Cures attributed to trichophytin for the most part concern infections due to M. lanosum, M. fulvum or T. gypseum, and since these have a tendency to spontaneous cure, the role of trichophytin is debatable. We have not been able to substantiate the claims made by a commercial concern for an imported trichophytin which has been extensively advertised as a certain cure for ringworm of the scalp. The cases of patients reported cured with estrogens by Poth and Kaliski were probably due to M. lanosum. In a study by Lewis, Hopper and Reiss of the effect on fungi of estrogenic and androgenic substances, an in vitro effect was apparent, but clinical results were poor when such agents were applied locally to areas of infection.

(*1*) *Manual epilation and local applications.*—When there is only a small patch (as revealed by examination under filtered ultraviolet rays), epilation of the infected hairs with forceps may be attempted. The process is repeated at intervals of three or four days. During the interval between treatments, adhesive plaster, larger in diameter than the infected patch,

should be kept constantly over the treated area. We have found that this not only prevents spread of the infection but tends to set up follicular irritation valuable in furthering cure. If the reaction to the adhesive plaster is too severe, it may be applied only part of the time. When the adhesive is left off the scalp, some fungicidal ointment should be used and a linen cap applied. The rest of the scalp should be treated with ointment containing 10 per cent ammoniated mercury applied morning and night. Shampoos are allowed, but the ointment is reapplied immediately after them. If the area of infection is large or if there are many different patches, manual epilation is not practicable.

Schwartz reported successful treatment of tinea capitis due to M. audouini using the following formulas:

1.	Salicylanilide	5
	Hyamine 1622 (25 per cent)	5
	Carbowax 1500	100
2.	S. S. copper undecylenate in carbowax	1500
3.	Pentachlorphenol	1
	Carbowax 1500	100

One of these remedies is applied daily for at least 40 days before improvement should be expected. Cure may not be obtained before 100 or more applications. A better effect was obtained in some instances by alternating the prescriptions.

(2) *Roentgen epilation.*—The use of roentgen rays by those competently trained has proved of infinite worth in the treatment of the resistant forms of tinea capitis. The incidence of infection in France, England and other countries has been materially reduced, and this treatment has been of marked economic importance in controlling the disease. A word of caution, however, is in order. The epilation of hair by means of roentgen rays is a most delicate operation, requiring considerable patience, special training and skill. The machine must be accurately standardized, and the technic of the operation should be learned thoroughly under the personal supervision of an authority. The reader is referred to Chapter XXVII in MacKee and Cipollaro's *X-Rays and Radium in the Treatment of Diseases of the Skin* for further details of technic. It may be emphasized that after the epilating dose of roentgen rays, the patient should be given an ointment containing 3 per cent ammoniated mercury. When the hair begins to loosen (after 18 to 21 days), daily shampoos are in order, and the hairs which cannot be epilated readily (as noted under the filtered ultraviolet rays) should be removed manually. The removal of adhesive tape applied to the scalp assists depilation at this time. The patient should not be discharged before two examinations under the filtered ultraviolet rays, made one week apart, have indicated normal conditions. A final inspection one month later is advisable. In pa-

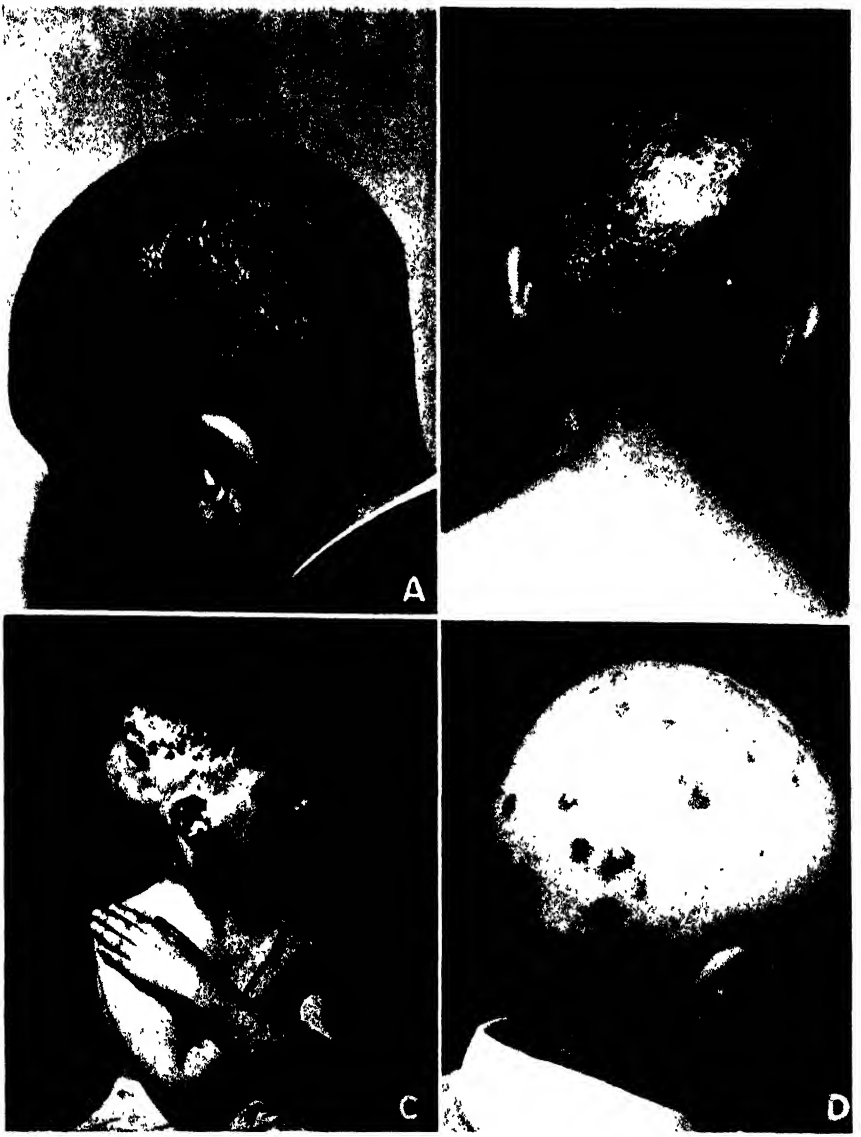

FIG. 15. Activation of tinea capitis which may follow x-ray therapy or develop spontaneously. *A*, tinea capitis due to M. audouini before x-ray therapy, showing gray-patch, relatively noninflammatory lesions. *B* shows severe inflammatory, pustular eruption which appeared over the scalp three weeks after epilating dose of x-rays. Erythematous papular lesions were noted on the trunk and extremities. Such a complication occurs in less than 1 per cent of patients treated with x-rays. *C* and *D*, tinea capitis due to M. lanosum. In *C*, the flare-up of lesions with development of ids on arms and trunk was spontaneous; in *D*, the occurrence followed an epilating dose of x-rays.

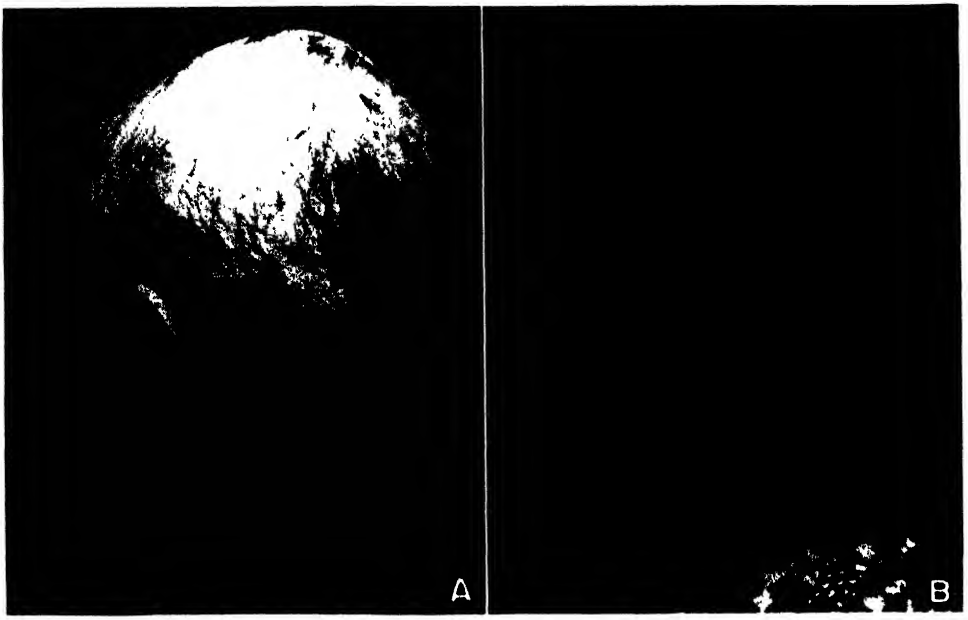

FIG. 16. Tinea capitis in an adult, showing results of x-ray therapy. *A*, 10 weeks after administration of epilating dose. *B*, six weeks later, showing uniform return of hair. Length from scalp is approximately 1.6 cm.

tients with a limited infection of short duration we have used roentgen ray epilation to only the affected site (one or two exposures). Care should be exercised that small foci of infection are not overlooked; we usually examine our patients several times, using filtered ultraviolet rays. The dose of roentgen rays administered should be one-tenth higher than that used with the

TABLE 15.—Return of Scalp Hair Following Administration of Epilating Dose of Roentgen Rays (figures based on average findings)

Elapsed Time, Mo.	Length of Hair, Cm.
2	soft down
3	1.0
4	1.3
5	1.9
6	2.7
7	3.8
8	4.4
9	6.7
10	7.0
11	8.6

five point technic. Following the treatment, a salve containing 3 per cent ammoniated mercury is used and should be reapplied twice daily to the entire scalp. The scalp should not be washed. After 21 days the grease may be removed by soap and water and by benzene and all loose hairs extracted by adhesive plaster. Negative findings from two Wood's light examinations one week apart should be recorded before the patient is discharged. It should be emphasized that this method is suitable only for special cases of limited infection, particularly in girls for whom total epilation of the scalp is a minor tragedy. Despite all precautions, the result may be a failure, in which case three months should elapse before further exposures are given.

(3) *Epilation by thallium salts.*—If a mistake is made in the dose of roentgen rays, permanent alopecia may result. A mistake in the dose of thallium acetate, however, may result in the death of the patient. Several instances of fatal mistakes are to be found in the literature. There is also the possibility of a number of other bad effects. The method consists in the oral administration of thallium acetate in a single dose of 8 mg. of the salt, dissolved in a glass of water, per kilogram of body weight. The exact weights of both the child and the drug should always be rechecked. There is definite contraindication to the treatment in the face of illness, particularly a renal ailment, in patients showing a disproportionate age-weight ratio and in adults. The after-treatment is that described for the use of

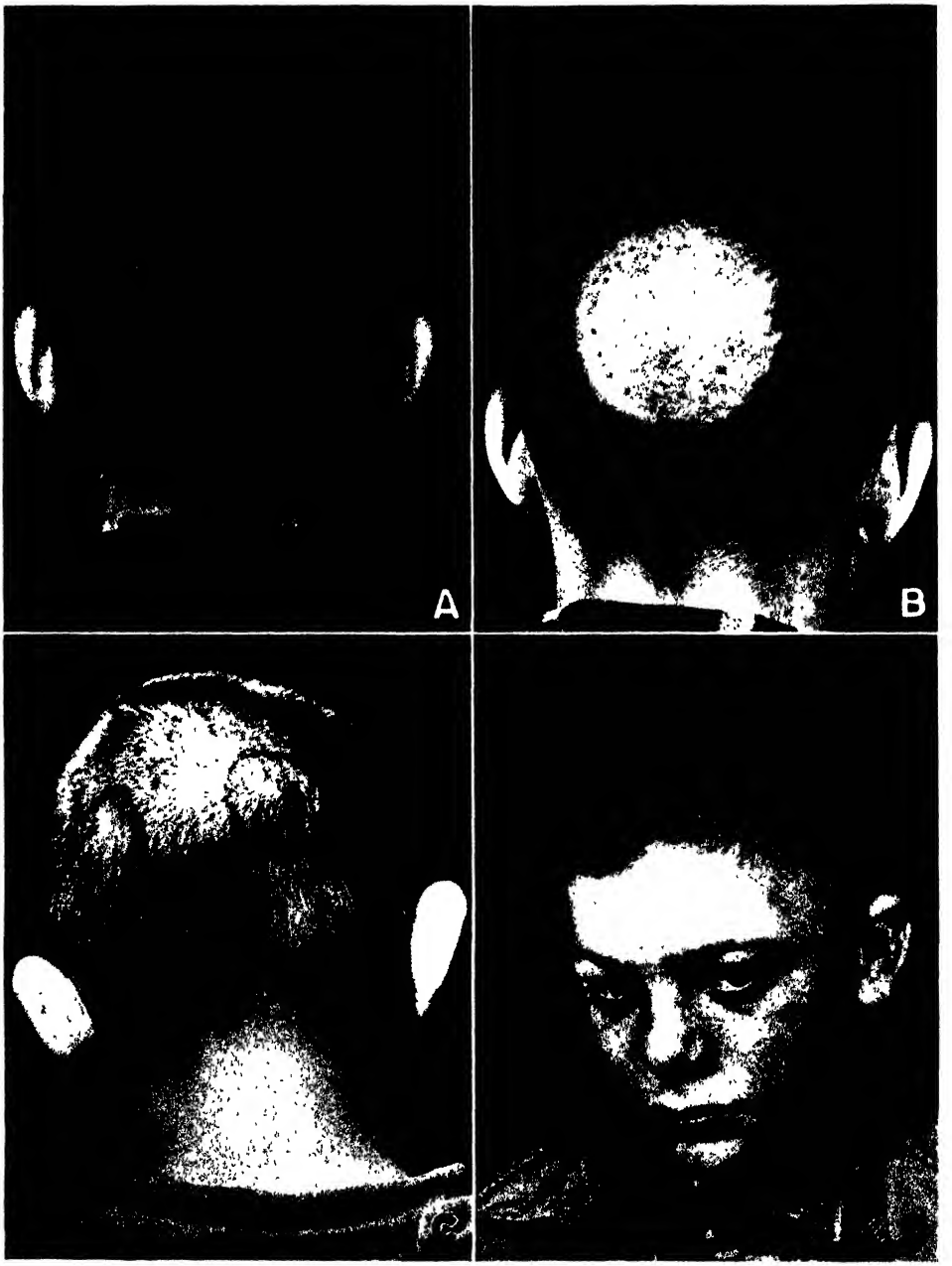

FIG. 17. Tinea capitis (M. audouini) of limited extent and recent origin treated successfully with x-rays to the localized infection. Careful attention to detail is necessary (see text). *A* and *B*, before and after preparation for treatment. *C*, two obscure lesions in occipital region outlined to reveal extent of fluorescent hairs. *D*, small localized lesion over left temple following epilation.

roentgen rays. Thallium epilation has been particularly recommended for the feebleminded and for those to whom the services of a trained roentgen technician are not available. It should again be mentioned, however, that the method is potentially dangerous, and one may question whether it should ever be used in the treatment of tinea capitis.

(j) TREATMENT OF ASSOCIATED CUTANEOUS LESIONS.—The patient should always be inspected for concomitant lesions. If any evidence of them is found, the use of an ointment containing 5 per cent ammoniated mercury or 0.25 per cent anthralin (dihidroxy-anthranol) will usually be sufficient.

(k) HOME CARE.—The following outline in mimeographed form is given to the parents of patients with scalp ringworm coming to the New York Hospital.

(1) The disease is contagious to other children. Because of this, bring to the clinic *all* other children in the family. They should be examined every three weeks even if well, until there is no more ringworm in the household. The patient should not go to the movies or barber shop and must not be sent to camp or play indoors with other children. He may play outdoors (with the scalp covered) provided an adult is present and no wrestling or games with personal contact are played. Please live up to these rules and help to stamp out this disease. As a precaution, any children in the family who are well should be cautioned against using the patient's comb, brush, hat or cap and should not sleep in the same bed with the patient. You should also rub through their scalps every night the salve which you will be given.

(2) The infection is deep in the hair and cannot be cured until the infected hair comes out. Sometimes x-ray treatment is necessary and sometimes not. The doctor will decide what treatment is best.

(3) You can help a lot in curing the patient by bringing the patient to the clinic at the appointed time and by following these directions.

(4) Rub in the salve, thoroughly, to all the areas outlined by the pencil. The remainder of the scalp should also be treated. Do this twice daily, morning and night.

(5) Do not wash the scalp with soap and water. This tends to spread the infection. The excessive accumulation of salve may be removed with mineral oil and absorbent cotton twice weekly.

(6) Make several linen skullcaps so the head can always be covered—even at night. Boil the caps for 10 minutes and change at least once daily.

(7) One type of ringworm is spread by infected pets, such as kittens and pups. If any animal pets are in contact with the patient, do not give the animal away or allow the animal his freedom so that other children may be exposed. The fluorescence test will decide if any infection is present.

Careful attention to directions will bring earlier cure and prevent infection of other children.

(l) PROPHYLAXIS.—The main consideration is to stamp out the resistant forms of the disease. Since these are usually spread by contact of one child with another, detection of all infected scalps is most desirable. The following precautions are important.

1. The medical examination before admittance to school should always

include a careful examination of the scalp. The use of filtered ultraviolet rays simplifies the examination and increases its accuracy and its rapidity.

2. Patients with ringworm should be excluded from school provided there is intelligent supervision of the child's activities at home. The danger to other children in the home or elsewhere is minimized if the patient constantly wears a linen cap.

3. Barbers should be told that infected combs and brushes will spread the infection. If the comb and brush were washed with soap and water after each use, this would probably be sufficient to prevent infection. The physician should not send a patient with tinea capitis to the barber shop. He might better remove the hair himself with hair clippers which he can sterilize. Barbers should be instructed not to cut the hair of a child with evidence of tinea capitis.

4. As this edition is being written, an epidemic of scalp ringworm due to M. audouini has been present for over four years in New York City. There is some evidence that the infection was spread in part from contact with the backs of theater seats, through the medium of barber shops and because of the overcrowding incidental to war and postwar conditions with rapid change of residence and lack of housing facilities. Some form of quarantine of infected children, so that other children are not exposed, may be requisite when such an epidemic occurs.

5. Parents should be instructed always to wash the child's scalp immediately after each haircut. The use of 5 per cent ammoniated mercury ointment before the shampoo would be additional protection.

6. Before admittance to a home or orphanage a child should be free from ringworm of the scalp, as shown under filtered ultraviolet rays.

7. Pets, particularly kittens, should be inspected under filtered ultraviolet rays, since they may be carriers of ringworm. The danger is probably greatest with stray animals.

8. Children must avoid persons known to be infected. This admonition would seem trite were it not for the many instances in which little concern was shown until the infection had been transferred from one person to another.

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2. TINEA BARBAE

Ringworm of the beard is rarely seen in the United States and is uncommon in New York. The infection is follicular; infection of the skin alone in the bearded region is not considered here.

(a) ETIOLOGY.—In the majority of cases the condition is due to T. gypseum. In a scattering of cases it is caused by M. lanosum, Trichophyton rosaceum, T. violaceum and T. purpureum. It is chiefly men who are vulnerable, and in many instances the barber shop has apparently been responsible for passing along the infection. Animals also play a part as carriers of T. gypseum or M. lanosum. In some instances the infection is caught from another person, not uncommonly a child with infection of the scalp or of the glabrous skin.

(b) SYMPTOMATOLOGY.—There are two types of infection, with dissimilar clinical pictures.

(*1*) *Kerion type.*—There is usually a history of contact with a diseased animal. When the infecting organism is T. gypseum or M. lanosum, the response is usually the development of one or more boggy infiltrations, particularly around the angle of the jaw. Any part of the beard may become infected, but the upper lip is an unusual site. The resemblance to kerion, as noted with ringworm of the scalp, is frequently striking. Hairs in the affected tissue loosen and either come out spontaneously or are readily extracted.

(*2*) *Sycosis type.*—When T. violaceum or T. purpureum causes tinea barbae, the infection gradually spreads, resulting in a mild pustular (crusted) folliculitis with breaking off of the invaded hair (T. violaceum) or similarly without the formation of hair stumps (T. purpureum).

(c) REACTION TO TRICHOPHYTIN.—Here, as with the other types of superficial fungous infection, the result of the intracutaneous test with trichophytin is dependent on the type of infecting micro-organism. If T. gypseum or M. lanosum is the causal fungus, there is usually a vigorous reaction; if T. purpureum or T. violaceum is responsible for the infection, negative or slightly positive reactions may be expected.

(d) FILTERED ULTRAVIOLET RAYS.—If M. lanosum or T. violaceum is present, fluorescence of the infected hair under these rays may be noticed. Since both T. gypseum and T. purpureum are ectothrix organisms, no fluorescence will be observed when they are present.

(e) DIFFERENTIAL DIAGNOSIS.—The kerion type of tinea barbae has to be differentiated from sycosis barbae, iododerma or bromoderma and syphilis. In sycosis barbae the lesions are rarely kerionic, the upper lip is frequently affected, and the hairs in the affected follicles are epilated with difficulty. Pustular reactions to one of the halogens is determined by the history, the tendency to bilateral involvement, the presence of the disorder elsewhere on the body and detection of the substance in the urine. Pustular syphilis is rare, doubly so if confined to the beard alone.

In all cases of tinea barbae the demonstration of the causal micro-

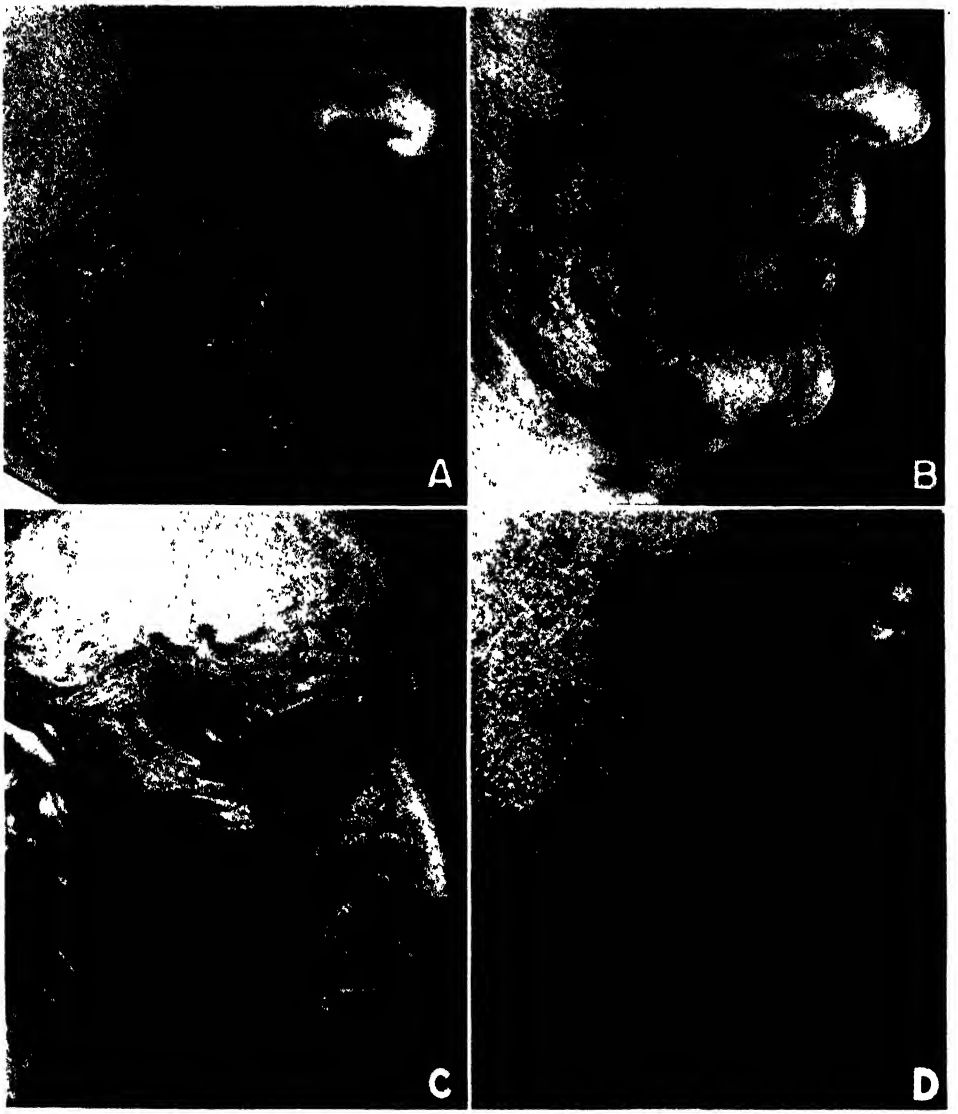

FIG. 18. Tinea barbae. *A*, T. gypseum infection before treatment. *B*, same patient following x-ray therapy and manual depilation. (*Courtesy of M. Silverberg.*) *C*, small follicular pustules due to T. purpureum. *D*, M. lanosum infection in a delicatessen worker.

organism is necessary to establish the exact diagnosis without equivocation.

(f) PROGNOSIS.—If the condition is of the kerionic type, there is good prospect of an early cure. If it is caused by T. purpureum or T. violaceum, other sites, such as the nails, are usually involved. The prognosis is to be reserved, depending on the co-operation of the patient and the type of therapy.

(g) TREATMENT.—When marked inflammation is present, the application of mild wet dressings, with use of such remedies as a 1:15 dilution of aluminum acetate (Burow's solution), hypertonic saline solution or solution of boric acid for as long periods as possible will assist drainage and prove soothing. The use of fractional roentgen therapy may be of value. Epilation by means of roentgen rays is seldom necessary or advisable. One should not use strong topical applications, particularly in the form of ointment. A number of other remedies, such as trichophytin and foreign protein shock, have been advocated but should be used with caution, since there is usually enough inflammation to cause the hair to loosen and cure to take place.

With infections of the beard caused by T. purpureum or T. violaceum, manual epilation repeated once weekly and the use of a fungicidal ointment, such as one containing 10 per cent ammoniated mercury or 0.25 per cent anthralin, may prove curative. Wise advocates manual epilation followed by hot dressings of Vleminckx's solution diluted 1:10. Unless attention is also paid to any other cutaneous manifestation, the condition will surely recur. If other foci of infection are present, it is questionable whether epilation of the beard by means of roentgen therapy should be undertaken. With this type of infection the use of trichophytin and foreign protein shock may be tried but will probably be ineffective.

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3. TINEA GLABROSA (CORPORIS)

(Ringworm of the Smooth Skin)

Superficial fungous infection of the smooth skin may occur as a scaly lesion, as a circinate patch, as a solid plaque or in a gyrate configuration. The manifestation may also simulate eczema, or deep granulomatous lesions may develop. We do not here include the intertriginous forms of

FIG. 19. Tinea barbae and sycosis barbae. *A* and *B*, tinea barbae due to T. gypseum. *C*, tinea barbae due to T. purpureum. *D* and *E*, chronic localized pyoderma. *F*, sycosis barbae.

infection (dermatophytosis, tinea cruris) or secondary allergic eruptions (dermatophytid). In many instances concomitant lesions will be found in the scalp, the nails, the bearded area, the inguinal region or the feet. A patient with an infection of the glabrous skin should be carefully examined for other foci.

(a) ETIOLOGY.—One of a number of different organisms may be found. The commonest is M. lanosum. The infection may be caught from a kitten or other pet, a playmate or another member of the household. Finding the source of infection here is usually comparatively simple. In other instances infection may be due to A. schoenleini, the condition almost always being secondary to an infection of the scalp; to T. gypseum, in which case the infection may have been caught from an animal, from a focus on the patient's feet or from another person, or to T. purpureum, the lesion in this instance almost always being part of a syndrome involving the nails and feet. During two years (1943 to 1945) we observed 18 cases of tinea of the nonhairy skin due to M. audouini, indicating that tinea glabrosa due to this fungus is more common than was formerly thought. There are a few other organisms which may at times produce eruptions on the smooth skin, but they are relatively unimportant. While these manifestations may appear at any age, children are particularly prone to exhibit circinate lesions due to M. lanosum. Adults, on the other hand, show a preponderance of infections due to the other organisms. Women occasionally become infected from their children or from new pets (kittens). One of the most obstinate cases of tinea glabrosa in our experience was that of a woman on whom developed over 100 circinate lesions and in whom the therapeutic response to various types of treatment was poor.

(b) CLINICAL TYPES.—(*1*) *Tinea circinata* (*M. lanosum and M. audouini*). —The classic form of ringworm is evidenced by an erythematous ringed lesion gradually increasing to a diameter not over 6 in. (15 cm.). There are usually minute vesicles along the border; the surface is scaly, and the center appears unaffected. Sometimes two or more concentric rings may appear in a single lesion. If the condition is untreated, new lesions develop on skin adjacent to or remote from the original focus. The lesions are commonly seen on the faces or necks of children with tinea capitis; while the infection is commonly due to M. lanosum, we have recently seen more cases than usual of tinea circinata due to M. audouini. The backs of the hands and other exposed parts are the usual sites of the first lesions in patients who catch the infection from an outside source. Ringed lesions are sometimes caused by T. purpureum. The subjective symptoms are usually mild, although the infection is itchy and subsequent scratching may contribute to its spread.

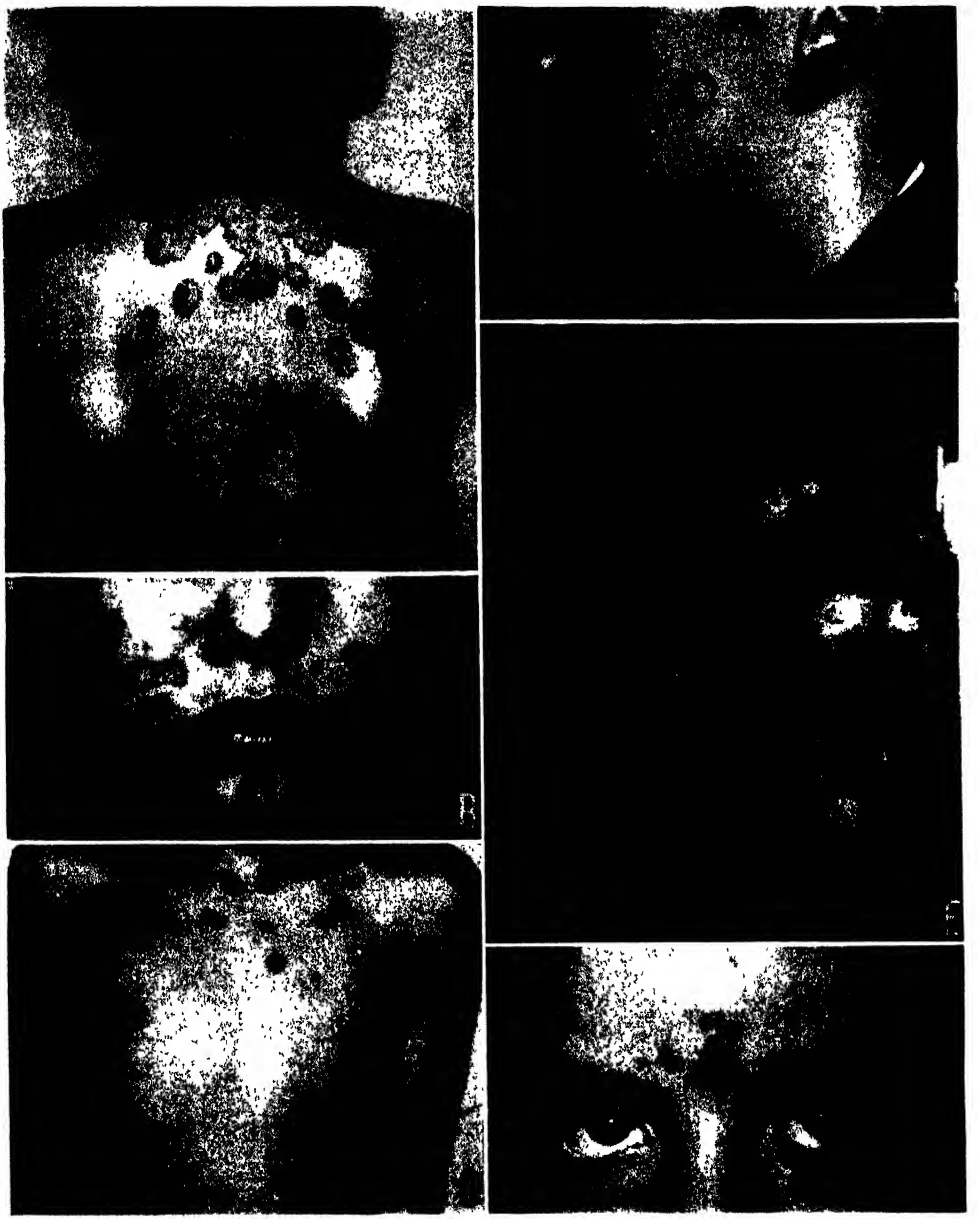

FIG. 20. Tinea glabrosa (circinate type) due to M. lanosum. *A, B* and *C* reveal disseminated lesions with a tendency to coalescence and double rings (an interesting immunologic phenomenon). *D,* common location for this type of ringworm. *E,* a dog belonging to the patient shown in *D;* these lesions yielded M. lanosum on culture. *F,* lesions of impetigo contagiosa. The ringed lesion on the forehead is suggestive of tinea, but there were typical crusted lesions elsewhere.

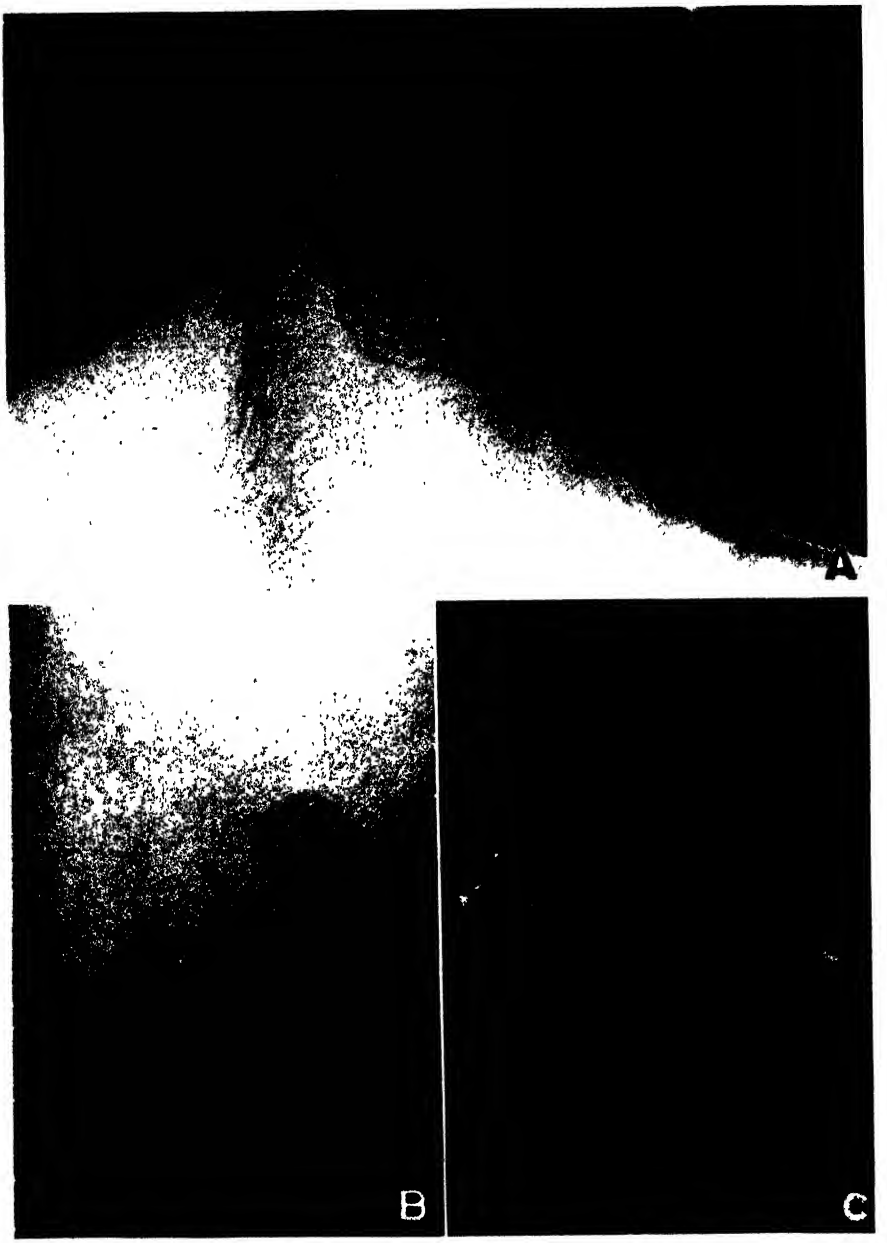

FIG. 21. Tinea glabrosa due to M. audouini. The lesions may be ringed or of the solid plaque type. Examination of lesions with filtered ultraviolet rays may reveal presence of infected lanugo hair; such hairs are difficult to epilate and contribute to chronicity.

FIG. 22. Tinea glabrosa and pityriasis rosea. *A*, typical circinate patches on the neck and chest with secondary satellite lesions (M. lanosum). *B*, ringed lesions with clearing centers. *C*, disseminated erythematous scaly lesions with accentuated border and clearing center. *D*, pityriasis rosea; the symmetry of the rash, the appearance of lesions in showers, the tendency of the lesions to follow the lines of cleavage and the negative results of examination for fungi usually serve to differentiate this disease from tinea circinata.

(2) *Eczematous type.*—There are two forms, primary and secondary. In the first, the initial response to infection (usually T. gypseum) is a vesicle, and vesicles continue to form, rupture and become crusted. The infection spreads peripherally; the lesion may remain ill-defined or become circinate, with active vesiculation along the periphery. There is no tendency to central clearing. Lesions are commonly solitary and rarely numerous. Included here is favus herpeticus, a rare manifestation of favus. The markedly inflammatory and rapidly spreading eruption due to Trichophyton alba may also be mentioned as an uncommon form. The secondary form of eczematous patch is caused by sensitization to applied medicaments or by treatment producing primary irritation, which transforms a circinate lesion into a vesicular, oozing patch.

(3) *Scaly type.*—A small area of ill-defined branny scaling with slight redness at the base may be the only manifestation of A. schoenleini or of one of the endothrix Trichophyta, such as T. violaceum. Trichophyton purpureum also causes such a lesion, but usually more typical areas are present in addition. Microscopic and cultural studies are necessary for differential diagnosis.

(4) *Crusted type.*—Favus of the glabrous skin may manifest itself by the formation of scutula similar to the cup-shaped crusted lesions commonly noted with the scaly type. Crusts may be formed by the drying of an exuding surface, particularly if the lesions are eczematous, but there is much more inflammatory reaction than is associated with favus.

(5) *Solid plaque type.*—Trichophyton purpureum is the cause of lesions which are not unlike certain lesions of psoriasis, being dull red and scaly on the surface, with slight thickening. Bleeding points are usually not present when the scales are removed. The intensity of the color may vary in different portions of a single patch. The shape of the lesions is not necessarily regular. The size of the patches varies from that of a pinhead to that of a half-dollar or larger. There is no tendency to central clearing. Lesions have been noted on various portions of the trunk, on the extremities and, in a single instance, on the face.

(6) *Bizarre and configurate type.*—In this type, T. purpureum is the cause of an eruption which may involve large surfaces of skin of the trunk. The infection begins at one or more points and migrates in a thin line over an ever-widening area. The affected skin is dull red and shows slight infiltration and scaling on the surface. Behind the advancing border the skin is lighter than normal. This suggests partial achromia. Persistent itching is a constant feature, and excoriations are usually seen.

(7) *Tinea imbricata-like type.*—Kittredge described a widespread scaly

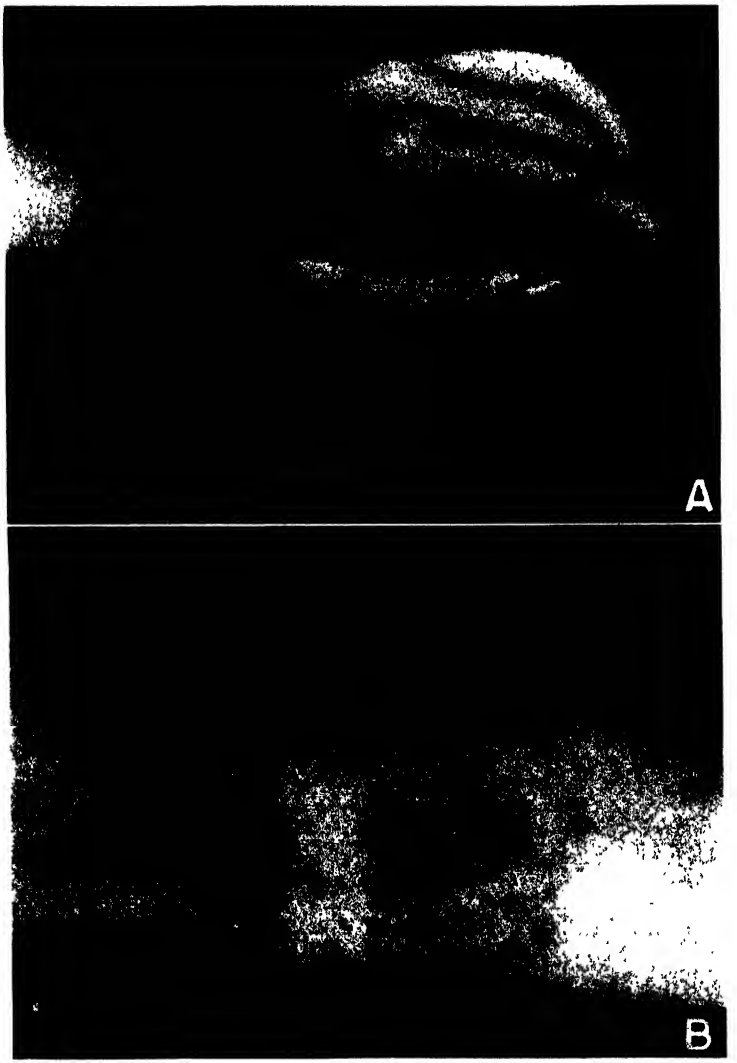

FIG. 23. Tinea glabrosa due to M. fulvum. There is usually a solitary lesion, predominantly observed in children.

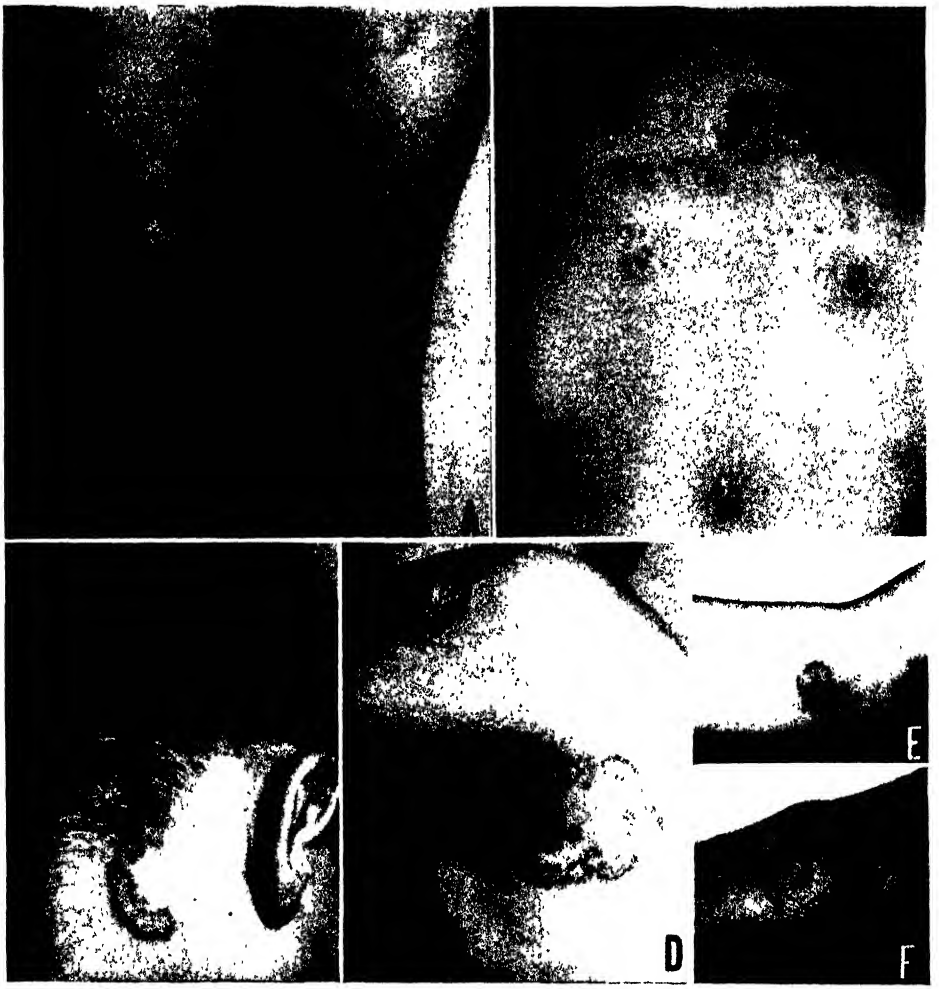

FIG. 24. Tinea glabrosa. *A*, disseminated erythematous scaly lesions on the arms and legs (M. lanosum). *B*, acute inflammatory (eczematous) lesions due to T. gypseum. *C* and *D*, gyrate and ringed lesions (T. violaceum). There were also lesions on the scalp. *E*, deep-seated infection on a wrist, the only lesion (T. violaceum). *F*, solitary ringed lesion on a wrist (T. sulfureum).

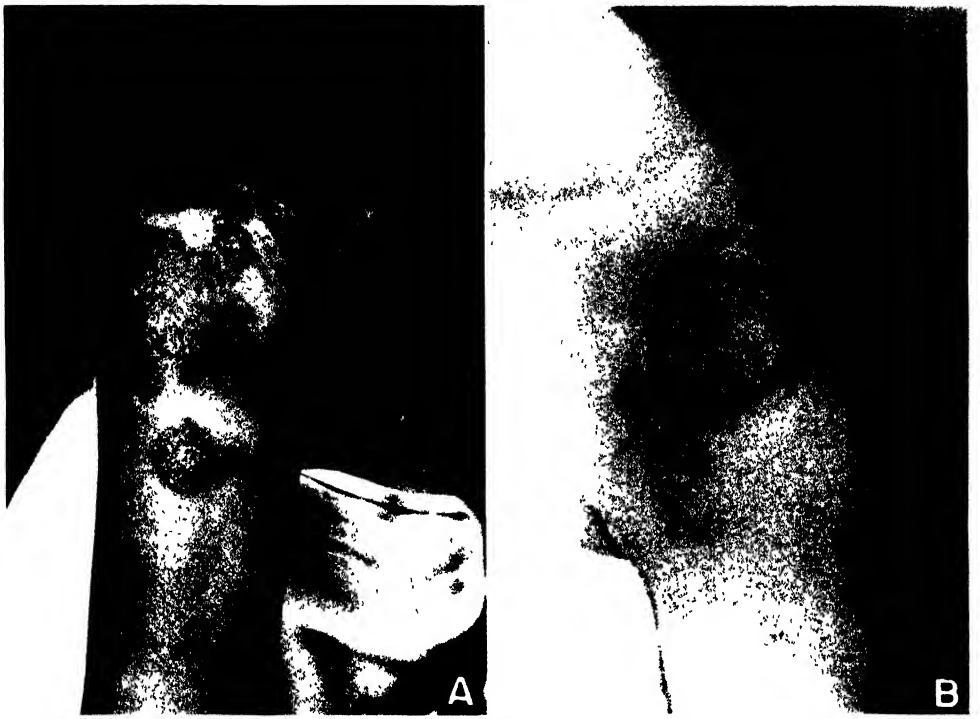

FIG. 25. Tinea glabrosa due to Trichophyton alba (faviforme) in sisters, aged 13 and 17. Rapidly spreading, boggy, inflammatory lesions are present. Since interchange of clothes was common, the development of lesions on identical locations (left shoulder) in both girls was considered to result from wearing an infected dress.

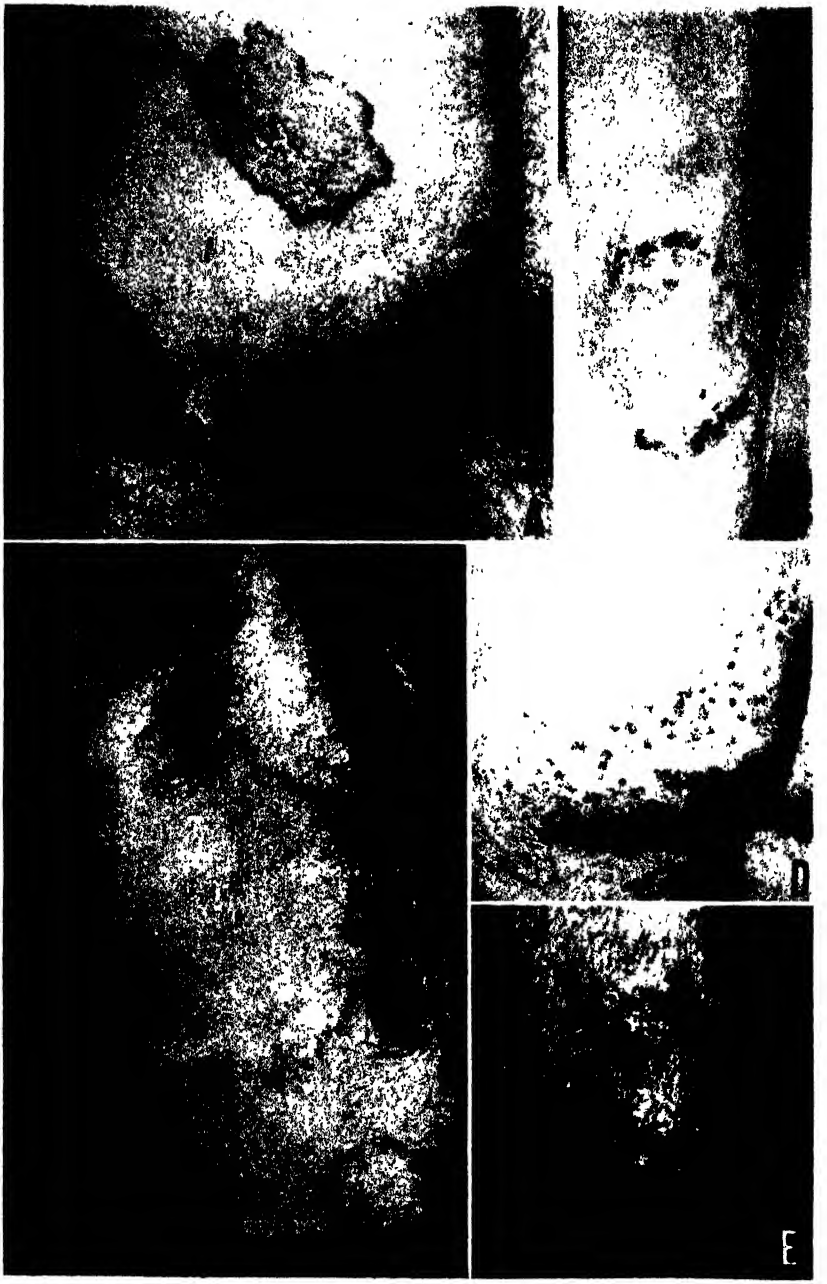

FIG. 26. Tinea glabrosa caused by T. purpureum. *A*, well defined, solid plaque type with little tendency to clearing. *B*, subacute, dull red plaque with vesicopustules at the periphery. *C*, annular and gyrate lesions. *D*, small, dull red, scaly, ill-defined patches. *E*, crusted, dull red lesions on the leg with involvement of the hair follicles.

eruption due to T. purpureum. The similarity to tinea imbricata was striking. We have observed several similar cases.

(8) *Granulomatous type (Majocchi), or tinea profunda.*—This is a rare but classic form of involvement in which the smooth skin may be involved separately or concurrently with the scalp or with the bearded area. There may be nodules and plaques, characterized by their indolent nature. Pus may collect and finally be discharged. Ulcers may develop, and small discrete nodules may appear in adjacent areas of skin also.

(c) IMMUNE REACTIONS.—The trichophytin reaction is usually negative in cases of uncomplicated tinea of the glabrous skin. This applies even to tinea circinata due to M. lanosum. For this reason the test is not of much practical value. Although we have no experience with reading the test when the condition is granulomatous, it is more than likely from analogy that there is an initiation of sensitivity in such a case.

(d) DIFFERENTIAL DIAGNOSIS.—Tinea circinata is simulated by pityriasis rosea when the herald patch is on the face or on an exposed portion of the body. The absence of a vesicular border, of clearing in the center or of the subsequent sudden development of secondary lesions is evidence against a diagnosis of tinea circinata.

The eczematous type is confused chiefly with contact eczema and sometimes with infectious eczematoid dermatitis or parasitic eczema. Contact eczema is usually differentiated by the history of exposure to a substance capable of causing the eruption, by the lack of circinate outline and at times by the patch test. In infectious eczematoid dermatitis there is a focus of infection, such as a boil or a discharging ear. The lack of definition of the lesions is a major point against tinea. Parasitic eczema consists of circumscribed vesicular erythematous patches, spreading apparently by autoinoculation. We recognize it as an entity but have never demonstrated fungi in material taken from the lesions. For this reason we doubt that the infection is fungous. The lesions, if examined closely, are seen to be studded with vesicopustules, and there is not the tendency to be present more abundantly along the border of the lesions.

The scaly type may be confused with seborrheic dermatitis, contact eczema or excessive dryness of the skin. The manifestation is so mild that a definite clinical diagnosis is usually impossible.

In order to prove the diagnosis of any of the types mentioned, one must demonstrate the causative micro-organism by microscopic and preferably by cultural studies. The clinical course may often be helpful, and the response to medication may be the only definite indication of the correctness of the clinical diagnosis when the mycologic examinations yield negative results.

Little difficulty will be experienced in the diagnosis of favus when typical scutula are present. The solid plaque type must be differentiated from psoriasis and from neurodermatitis circumscripta. The irregular distribution and the lack of bleeding points, together with other evidence of the infection on the feet and lack of involvement of the scalp, will serve to rule out psoriasis. Neurodermatitis circumscripta is more pruritic; there may not be a history of another allergic disease, and there is usually evidence of other forms of infection on the feet.

The bizarre and configurate type may be simulated by erythema annulare centrifugum (Darier), but the scales on the surface of the lesions, the intense itching, the absence of edematous plaques and the lack of temporary remissions are against the latter diagnosis.

Majocchi's granuloma may be mistaken for pyoderma, bromoderma or iododerma, one of the deep mycoses, such as sporotrichosis, or tuberculosis. The mycologic study may be the only definite method of determining the true nature of the condition.

(e) PROGNOSIS.—This varies with the infecting micro-organism. Ordinary tinea circinata usually responds to treatment within a week or two. The presence of infected lanugo hairs will retard recovery. The eczematous type requires a longer time for cure, but the final result is usually satisfactory. In the manifestations of A. schoenleini the prognosis is good provided treatment is continued for a long period. The infections due to T. purpureum are similarly resistant and should always invite inspection of other likely sites of the infection.

(f) TREATMENT.—Applications twice daily of an ointment containing 3 per cent salicylic acid and 5 per cent ammoniated mercury usually cause a lesion of tinea circinata to disappear within a week or two. Tincture of iodine (1 per cent) may be painted on the affected skin once daily, but not when ammoniated mercury is being used. Anthralin ointment (0.25 per cent) is useful but is irritating to a sensitive skin. For the eczematoid form, soothing treatment such as application of calamine lotion or, if exudation is pronounced, of dressings wet with a solution of boric acid or with dilute Burow's solution is the correct initial procedure. Roentgen therapy is useful in cases with exudative processes.

Infected lanugo hairs should be manually epilated. It is known that they often break off and for this reason repetition of hand epilating may be necessary.

In the manifestations due to A. schoenleini or T. purpureum, fungicides similar to those mentioned for ordinary tinea circinata may be used, but concentrations should be stronger. Compound ointment of benzoic acid is another useful preparation. The main point is to continue treatment, even

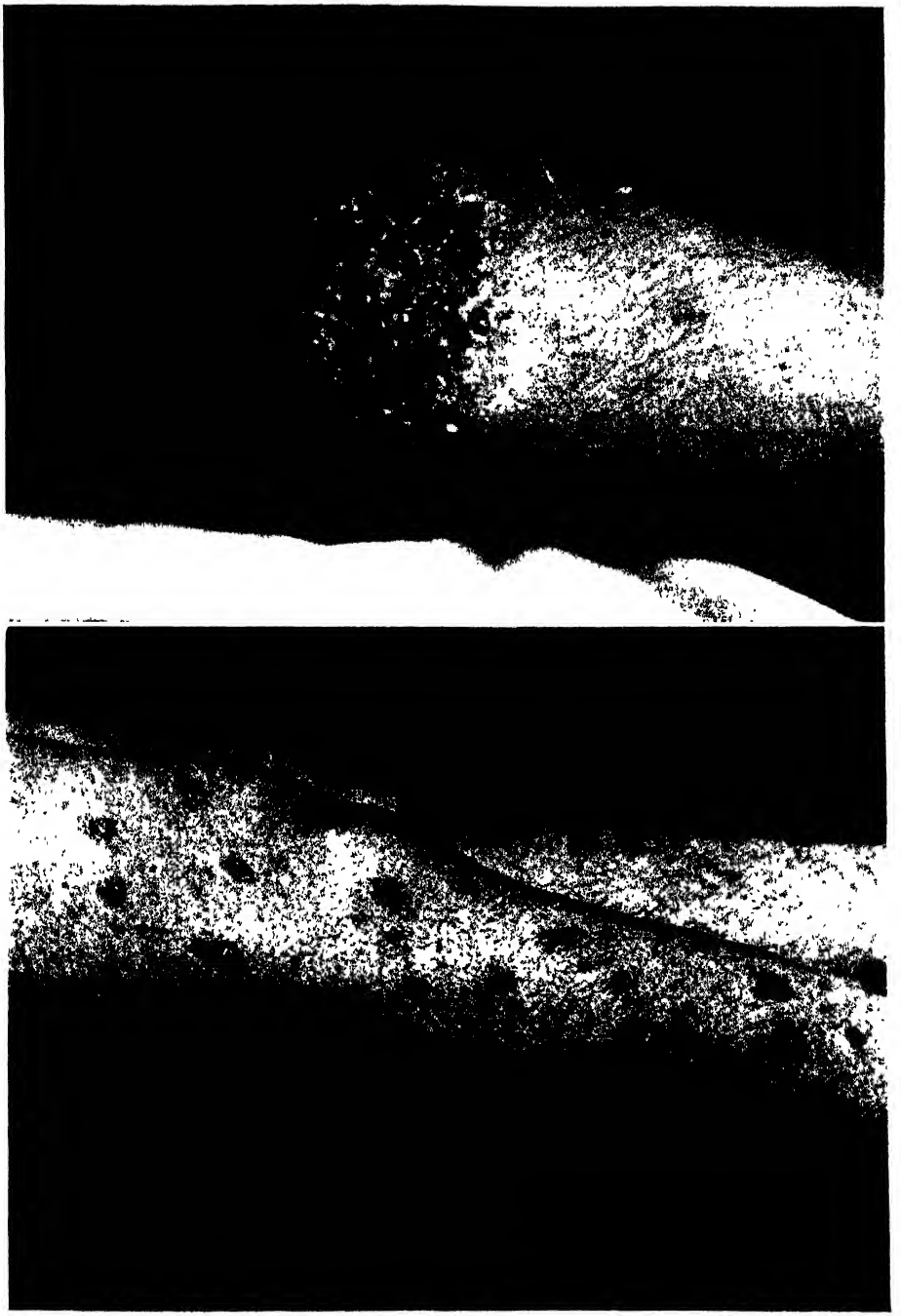

FIG. 27. Tinea glabrosa. *A*, granuloma majocchi—an example of a vigorous response to the infecting micro-organism (T. gypseum). *B*, disseminated erythematous crusted lesions due to A. schoenleini.

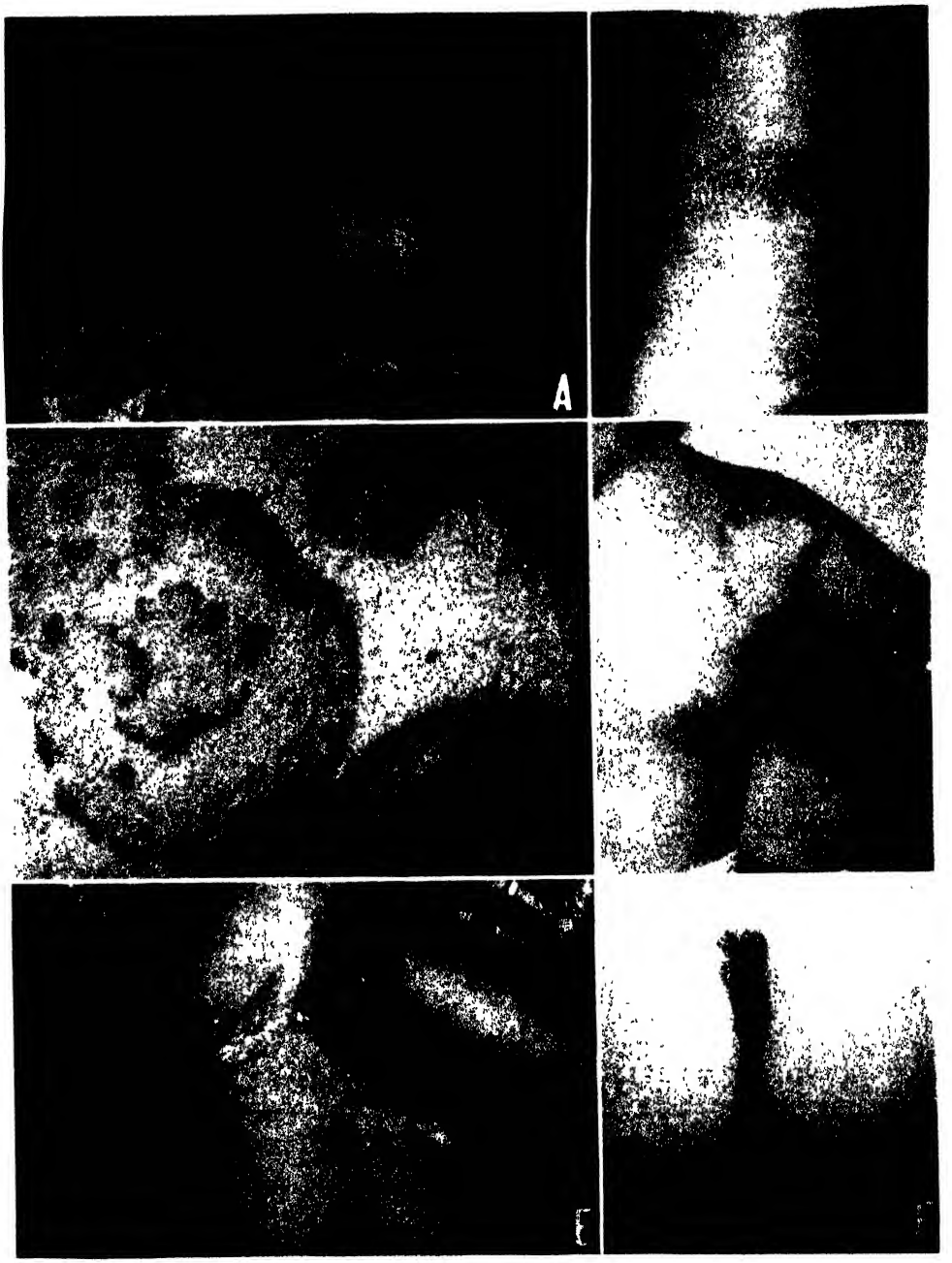

FIG. 28. Nonmycotic disorders often confused with fungous eruptions. *A*, disseminated neurodermatitis in a child with an allergic family history. When only the hands are affected, diagnosis is often difficult. *B*, lichen spinulosis, which is sometimes secondary to a fungous infection. *C*, erythema annulare centrifugum simulating the gyrate lesions caused by T. purpureum. *D*, psoriasis simulating tinea circinata. *E*, inframammary lesions of psoriasis resembling moniliasis. *F*, intergluteal patch of psoriasis.

after all vestige of the disease has gone, until cultures inoculated with material from the sites of the former lesions are sterile. It should also be a rule to examine the patient carefully for other evidences of the disease, since the body lesions are rarely the primary manifestations. In favus, the scalp is usually the initial site of infection; with T. purpureum the feet, groin or nails are usually concomitantly infected. In case of a deep infection (Majocchi's granuloma) filtered roentgen therapy should be administered, wet dressings applied and the iodides prescribed for internal use. Salves seldom help.

We do not now use or recommend the use of ultraviolet rays or injections of trichophytin in the treatment of tinea glabrosa.

In rare instances there is a complete absence of resistance to infection on the part of the patient. This may rarely occur in cases of infection with fungi that ordinarily cause acute inflammatory responses in the patient's skin. Hazel and Lamb recorded the case of a girl, 23, who had gastrointestinal moniliasis and coincidentally a cutaneous rash due to M. lanosum. The latter eruption was widespread on the face and body; the fingernails and toenails were involved. The M. albicans infection was of 14 years' duration; the manifestations of M. lanosum had been present for seven years. Every possible form of therapy was administered without any consistent effect. We have observed several instances of resistance to treatment when cultural studies revealed a fungus which ordinarily responds satisfactorily within a short while. Fortunately, instances of stationary infections, such as that of the patient of Hazel and Lamb, are rare.

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4. TINEA CRURIS

This is a superficial fungous infection usually confined to the inner surface of the upper parts of the thighs. There may be contiguous spreading, or other parts of the skin may become affected. In India the ailment is known as dhobie itch. It is sometimes still referred to as eczema marginatum, under which term it was first described by Hebra in 1860.

(a) Etiology.—The classic form of the disease is caused by E. inguinale (floccosum). It may be spread by infected articles of clothing or by an athletic suspensory, but at times the exact method of dissemination is un-

known. There have been epidemics, such as that reported by Mercer and Farber. The localization is in part explained by the affinity of the fungus for intertriginous areas. The crural region may also be the site of mycotic infections due to T. gypseum and T. purpureum.

(b) IMMUNOLOGIC REACTIONS.—Epidermophyton inguinale usually does not initiate sensitization to trichophytin. A test with trichophytin usually elicits a negative or a mildly positive reaction. With T. gypseum, a positive reaction is usual, but when T. purpureum is the causative fungus, a negative reaction is common.

(c) CLINICAL DATA.—The rash is well marginated, the surface is scaly, and the border shows minute vesicopustules. There is little or no tendency to central clearing. The color of the lesions is brownish, with some redness due to inflammation. The eruption is usually bilateral and symmetrical; it favors the upper inner portions of the thighs but may extend up to the pubis and as far back as the sacrum. The genitalia may share the infection. According to Hopkins, the scrotum was commonly affected in patients he studied at Fort Benning. The axillas, the umbilicus, the inframammary areas and the interdigital webs of the feet are occasional sites of the infection. Vesicopustules are sometimes seen on the soles. With the friction of clothing, especially during the heat of summer, varying degrees of secondary eczematization occur. Follicular involvement is unknown. We have never found E. inguinale in nail tissue.

In cases of infection with T. gypseum, the feet are usually previously involved, and inflammation is more marked, as evidenced by vesiculation and exudative patches. The localization to the strictly intertriginous parts is more pronounced. With infections due to T. purpureum, dull red, scaly, thickened plaques may be found in the crural region as part of a widespread eruption. Itching is more marked than when the infection is due to E. inguinale or to T. gypseum. The distribution is usually unilateral, in contradistinction to the type caused by E. inguinale.

(d) DIFFERENTIAL DIAGNOSIS.—There may be some confusion with erythrasma and moniliasis, particularly when areas other than the groins are affected. The red border of the former disorder and the moist character of the latter are distinguishing features. Psoriasis and seborrheic eczema may also be simulated, but these diseases are rarely confined to this location.

(e) PROGNOSIS.—The ordinary form of the disease usually responds readily to medicinal applications. Relapse is common; it is probably due to ill-timed stopping of the treatment or to reinfection from untreated parts or from clothing. The lesions caused by T. gypseum are likewise readily cured, but those due to T. purpureum are extremely obstinate to all

FIG. 29. Tinea cruris. The bilateral rash with well defined elevated edge and scaly surface is characteristic. Culture yielded E. inguinale.

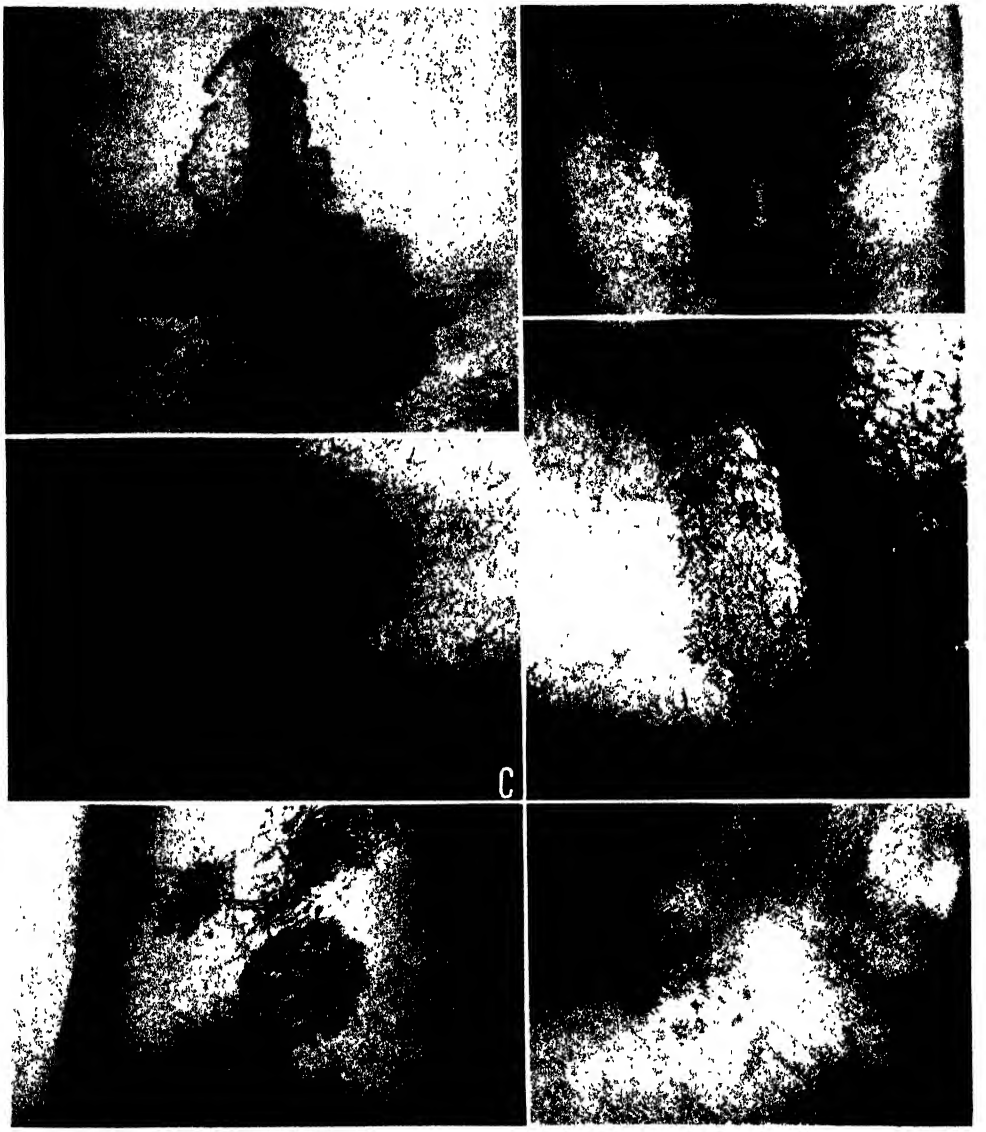

FIG. 30. Tinea cruris. The classic cause is E. inguinale. However, in not all cases is tinea cruris caused by this species of fungus. Epidermophyton inguinale may also cause lesions in adjacent or remote parts of the skin. *A*, *B* and *C*, lesions caused by T. purpureum; cure is difficult. *D*, rash on the inner part of the thigh caused by E. inguinale. *E* and *F*, superficial circinate vesicular lesions in the axilla and on the dorsum of the foot (of the same patient); E. inguinale was isolated from both lesions.

forms of treatment and may soon recur if preventive therapy is abandoned.

(f) TREATMENT.—Against the ordinary form of the disease (due to E. inguinale), one of the following topical applications may be used.

1. Salicylic acid, 3 per cent and precipitated sulfur 6 per cent in equal parts of lanolin (hydrous wool fat) and petrolatum. It is advisable to begin with this concentration, but if on the next visit there is no evidence of irritation, the strength of both drugs may be doubled. With nightly applications of this ointment the patient is usually cured in about three weeks.

2. Resorcinol, 3 to 12 per cent in lotion of zinc oxide, is advocated by Wise. The peeling effect of the resorcinol is tolerated better in this medium than in a grease.

3. Compound ointment of benzoic acid (Whitfield's ointment) may be used, with 3 per cent salicylic acid and 6 per cent benzoic acid. If there is no cutaneous reaction, the strength of the ingredients may be cautiously increased.

It is inadvisable to use chrysarobin or thymol in this location unless previous medication is unavailing. When there is marked inflammatory reaction, soothing applications should first be applied. A 1 per cent aqueous solution of gentian violet (methylrosanilin) may be painted on the affected skin. If the infection is still present after the inflammatory reaction has subsided, one of the aforementioned prescriptions may be used. There is no indication for the use of roentgen or ultraviolet rays. We have never seen any benefit from the therapeutic use of trichophytin.

The treatment of an infection due to T. gypseum or to T. purpureum has been considered in the following section on dermatophytosis.

Intertrigo of the groin due to M. albicans may also be confused; its treatment is discussed under moniliasis.

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5. DERMATOPHYTOSIS (DERMATOMYCOSIS, INCLUDING ONYCHOMYCOSIS)

The term dermatophytosis is commonly used in this country to refer to a superficial fungous infection of intertriginous or flat areas of skin. We here include under this heading tinea pedis, secondary lesions acquired by contact with lesions elsewhere on the body, particularly on the hands

(tinea manuum), and allergic manifestations, or dermatophytids. Fungous infection of the nails (tinea unguium, or onychomycosis), which is caused by the same species of fungi, is usually described as a separate entity. The involvement of nails is linked so intimately with that of the feet that we believe it should be included as part of the syndrome. The usual varieties of infection of the nails are discussed in this section. Ungual and paronychial infections due to M. albicans are described in the section on moniliasis, pp. 145 ff. We agree with Weidman that dermatophytosis of the type caused by T. gypseum is essentially an intertriginous condition and usually begins as such. Associated, however, are sensitization or the lack of it, secondary infection, acuteness or chronicity and a number of important incidentals. The terms epidermophytosis, epidermomycosis and trichophytosis are also used by some as synonyms for dermatophytosis but would better be reserved for instances of specific infection (as epidermophytosis: due to E. inguinale).

(a) INCIDENCE.—It has been variously estimated that from 50 to 90 per cent of the population of the United States are affected at some time during their lives. Hulsey and Jordan recorded a clinical incidence for tinea pedis of 67 per cent and a microscopic incidence of 63 per cent in a series of 100 university students. Gilman noted that of 390 new patients with diseases of the skin seen during six months in the Student Health Service of the University of Pennsylvania, 145 (37 per cent) had a mycotic infection. The average age of these patients was 19½ years. Gilman examined 500 students; 297 (60 per cent) had gross evidence of ringworm. Legge, Bonar and Templeton found that 53.3 per cent of the men and 15.3 per cent of the women of the 3,100 freshmen in a university were infected and that at the end of the spring semester 78.6 per cent of the men and 17.3 per cent of the women had tinea pedis. Muskatblit examined 112 medical students and 100 dispensary patients. Evidence of dermatophytosis was presented by 89 per cent. Andrews and Birkman in a clinical study of 520 public school students between the ages of 14 and 20 noted that 65 (12½ per cent) showed clinical signs of fungous disease. We can substantiate the relative infrequency of Trichophyton infection in adolescents and in children. Prehn found that 88 per cent of 1,500 men examined on 11 ships of the United States Navy showed clinical evidence of ringworm of the feet. In a survey of over 300 patients in a home for the aged we found evidence of residual infection in the skin and nails of over 90 per cent; only a few of the patients complained of the condition. Ajello, Keeney and Broyles stated that 40 per cent of young men entering military life had normal feet, whereas for the troops at Fort Benning, Hopkins and his coworkers reported normal findings in only 20 per cent when the feet were

examined painstakingly by clinical, microscopic and cultural methods.

(b) HISTORICAL SURVEY.—According to Ormsby, ringworm of the hands was noted by Tilbury Fox in 1870 and by Pellizari in 1888. The first detailed study of ringworm as it affects the hands and feet was that of Djelaleddin-Moukhtar in 1892, and credit should be given him for timely and accurate observations. Whitfield, Sabouraud and Kaufmann-Wolff made early reports.

In this country, Ormsby and Mitchell were the first to report a comprehensive series of cases of ringworm of the hands and feet. Many investigators have since reported their findings. A selection will be found in the bibliography. Weidman's article (1927) was, and still is, the most important published on this subject in the American literature. The literature on this subject has been enriched by the exhaustive researches and careful, painstaking observations and deductions of J. Gardner Hopkins and his group. The studies were carried out from 1942 to 1945 at an infantry post, Fort Benning, Georgia.

Allergic secondary lesions (dermatophytids) were described by Jadassohn and others of his school as emanating from a deep focus such as an infection of hair follicles. C. M. Williams first showed that similar lesions can be present on a localized part of the body (usually the fingers and palms) when the primary focus is on the interdigital webs of the feet. This observation has been substantiated by Peck, Walthard and many others.

Hodges' report in 1921 focused attention on the disease as it affects nails.

(c) ETIOLOGY.—Two organisms, T. gypseum and T. purpureum, cause the bulk of the infections (Table 16). Whereas in civilian life, E. inguinale

TABLE 16.—RESULTS OF CULTURE OF MATERIAL FROM THE FEET OVER A FIVE YEAR PERIOD (1942–46 INCLUSIVE)

ORGANISM	NO. OF CASES	PERCENTAGE OF CASES	PERCENTAGE OF ORGANISMS
T. gypseum	247	30.4	47.4
T. purpureum	217	26.7	41.7
E. inguinale	35	4.3	6.7
M. albicans	22	2.7	4.2
No growth	292	35.9	
Total	813	100	100

is relatively uncommon as the cause, Hopkins and his co-workers reported an incidence of 17 per cent in soldiers; they found T. gypseum in 47 per cent and T. purpureum in 36 per cent of positive cultures. M. albicans may also cause intertrigo of the toes, and in rare instances M. lanosum and several other dermatophytes have been cultured. Occasionally lack of results from culture when a condition was clinically thought to be dermatophytosis has led some observers, including ourselves, to believe that strepto-

cocci (which are occasionally present) and perhaps some of the ordinary saprophytes of the skin may cause the condition. This is purely speculative. We have reported 23 cases of multiple fungous infections with 12 different combinations of pathogenic fungi. Although some difficulty was encountered in deciding the role of the pathogenic species isolated from diseased tissue, in nine cases it was decided that the fungi present were in symbiosis. Multiple fungous disease is probably not uncommon. In the majority of cases infection of the nail is also caused by T. gypseum or T. purpureum. Achorion schoenleini and several other fungi are occasionally found. Cases of infection due to M. albicans are discussed in the section on moniliasis (pp. 145 ff.). While the toenails are usually infected secondarily to an interdigital infection of the feet, the fingernails may or may not be involved after infection in another site. In some instances the evidence points to a primary infection of the fingernails due to poor hygiene during a manicure. In many instances the method of infection is unknown. Hodges estimated that in the Southern states the prevalence of tinea unguium is 1 to 500 of the population. Incidence is at least as great in New York.

The disorder is rarely seen in children. The most vulnerable age period seems to be from the sixteenth to the twenty-fifth year. Primary infections usually appear during these most active years. The manifestations of the disease in later years, while common, may usually be placed in the category of flare-up, or exacerbation.

The disorder is seen much more in males than in females. This may be due in part to more particular hygiene on the part of women or to the greater chance of contamination of men due to their greater interest in athletics and to their congregating in camps, clubs and gymnasiums, with the common use of locker rooms, shower baths and other facilities. There must be still another reason why many wives who were exposed prior to the knowledge of the contagiousness of the condition failed to become infected. It seems that men are more vulnerable. There was an apparent increase in the incidence of disabling dermatophytosis among the members of the armed forces in World War II over incidence in the same age group in civilian life. This is not unexpected, despite improved methods of therapy, for the troops walk in bare feet over floors bound to be infected, there is common use of bathrooms, hygiene is poor during combat service and trauma and sweating after long marches are conducive.

The disease is more prevalent in the summer. We observe fewer cases in New York in the winter than in the summer, and the character of the disease varies considerably with the season. In summer, exceedingly acute involvement occurs more often, and there is generally more inflammation.

Hyperhidrosis is a common finding in patients with dermatophytosis. Just how much the sweat has to do with the furtherance of the infection has been the subject of study of a number of investigators. Levin and Silvers showed that fungi will grow in sweat. Peck has found that true sweat has fungistatic power not possessed by insensible perspiration. The latter, when present to excess, produces maceration of the skin, which accordingly is more vulnerable to the invasion of fungi. The alkalinity or acidity of the sweat may play a part in the predisposition toward infection. The diet, the amount of sweat secreted and the amount of evaporation are factors in the pH of the sweat.

Lowering of a patient's vitality during a debilitating illness may be reflected in a predisposition to the disease. A quiescent interdigital infection may become inflammatory and spread to adjacent and remote cutaneous areas.

In many instances, predisposing factors may not be manifest, and we are forced to conclude that infection may often take place when normal persons come in contact with pathogenic fungi. An abrasion may provide a portal of entry, but even that is apparently unnecessary in most cases.

The main factor in ascertaining the etiology and consequently the prophylaxis of the condition is determination of the reservoirs in order that they may be eliminated. The chief foci are to be found on the feet of carriers, who are unaware of the disease or are careless in treating it. That pathogenic fungi may remain viable for some time in a dry state has been proved by Farley, Weidman, Mitchell and others. Weidman calculates that many pathogenic fungi may survive in the dry state from approximately six months to a year. Fungi of pathogenic titer have been yielded by cultures of material from floors, mats and gymnasium apparatus (Williams), shoes (Jamieson and McCrea), cotton, linen, silk (Hruszeck-Kadisch), wool and silk and many different woods and in the presence of moisture (Bonar and Dreyer). Goldman mentioned that spores of fungi have been carried nearly 14 miles (22 kilometers) up into the stratosphere and have survived cold, solar radiations and other extreme conditions. Fortunately, however, the spores of fungi are not as resistant as those of bacteria. Moreover, they are readily destroyed by heat. Weidman found that most species of fungi in culture and in scrapings were killed by exposure to a temperature of 48 C. for 10 minutes.

(d) IMMUNOLOGIC REACTIONS.—This topic is discussed at length in Chapter VI, "Immunity and Cutaneous Sensitization." The practical importance of the routine use of the trichophytin test in connection with other studies is well recognized. Initiation of sensitivity 48 hours after the test occurs in about 70 per cent of patients infected with T. gypseum, while only 30

per cent of those infected with T. purpureum have a positive reaction after 48 hours. With the latter infection an immediate wheal reaction to trichophytin may be expected in about 40 per cent of patients. With the acute form of ungual involvement due to T. gypseum, there may be initiation of cutaneous sensitivity, as evidenced by the development of a reaction to trichophytin. The superficial type (leukonychia trichophytica) and the infections due to T. purpureum seldom have the ability to sensitize. The same is true of ungual infections due to A. schoenleini.

(e) CLINICAL CHARACTERISTICS.—There are two chief forms of the disorder, namely, (1) the inflammatory type, due to T. gypseum, and (2) the chronic type, due to T. purpureum. Since there is a wide difference in the appearance, behavior and response to treatment of each, they will be taken up separately.

(*1*) *Inflammatory type* (*Trichophyton gypseum*).

A. Involvement of the skin. The disease commonly makes its appearance on the feet in the form of vesicles on an interdigital web, on the sole or on both.

In the first-mentioned location the vesicles, or bullae, rupture readily, and the skin at the site of the lesion becomes macerated and soggy. The process is usually associated with a certain degree of erythema, but this may be lacking. The condition may remain in this stage for weeks, months or years. On examination some maceration and peeling may be noted. The development of fissures or cracks is common. For some reason not yet known the web between the fourth and the fifth toe is particularly vulnerable. In this stage the inflammatory form may be indistinguishable from the chronic type (due to T. purpureum).

With favorable conditions the disease may assume a more inflammatory character. This usually occurs during the summer season, although not exclusively. The first indication may be pruritus of the toes accompanied by some swelling (edema) and followed by appearance of vesicles. The soles may be the chief areas affected, but if the inflammation is violent, vesicles may appear on the sides of the toes and feet. Owing to scratching and trauma from local applications (self-medication being exceedingly common) there is an increase in the inflammatory reaction, and secondary pyogenic infection may appear. Coincidentally with the increase in the local inflammation on the feet and frequently with the development of lesions on the soles, vesicles may appear at a site or sites remote from the original infection. The hands (particularly the palms and sides of the fingers) are chiefly affected. This type of eruption is due to the dissemination of products of fungi through the blood stream, and the lesions are known as dermatophytids. This subject is considered in more detail on pages 116 to 119.

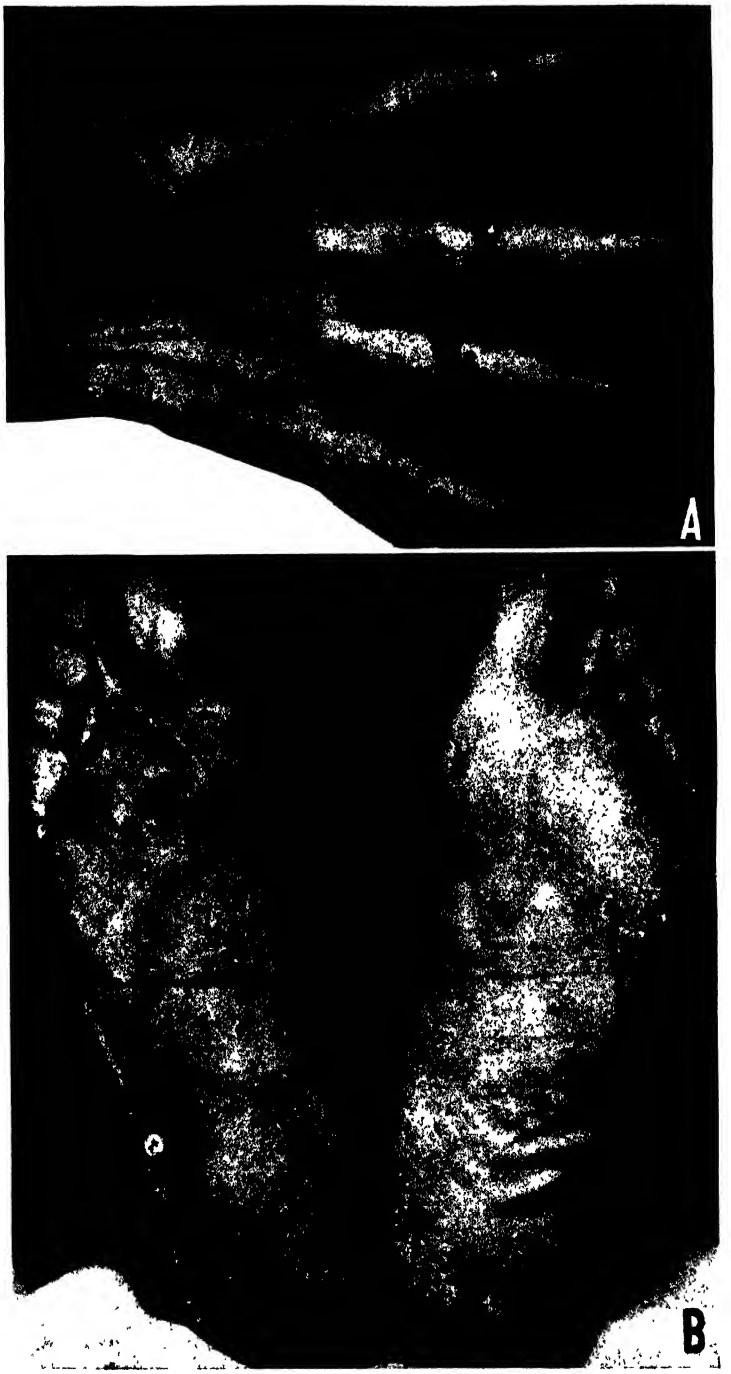

FIG. 31. Dermatophytosis of the acute type affecting the hands and feet. Trichophyton gypseum was repeatedly isolated from both sites.

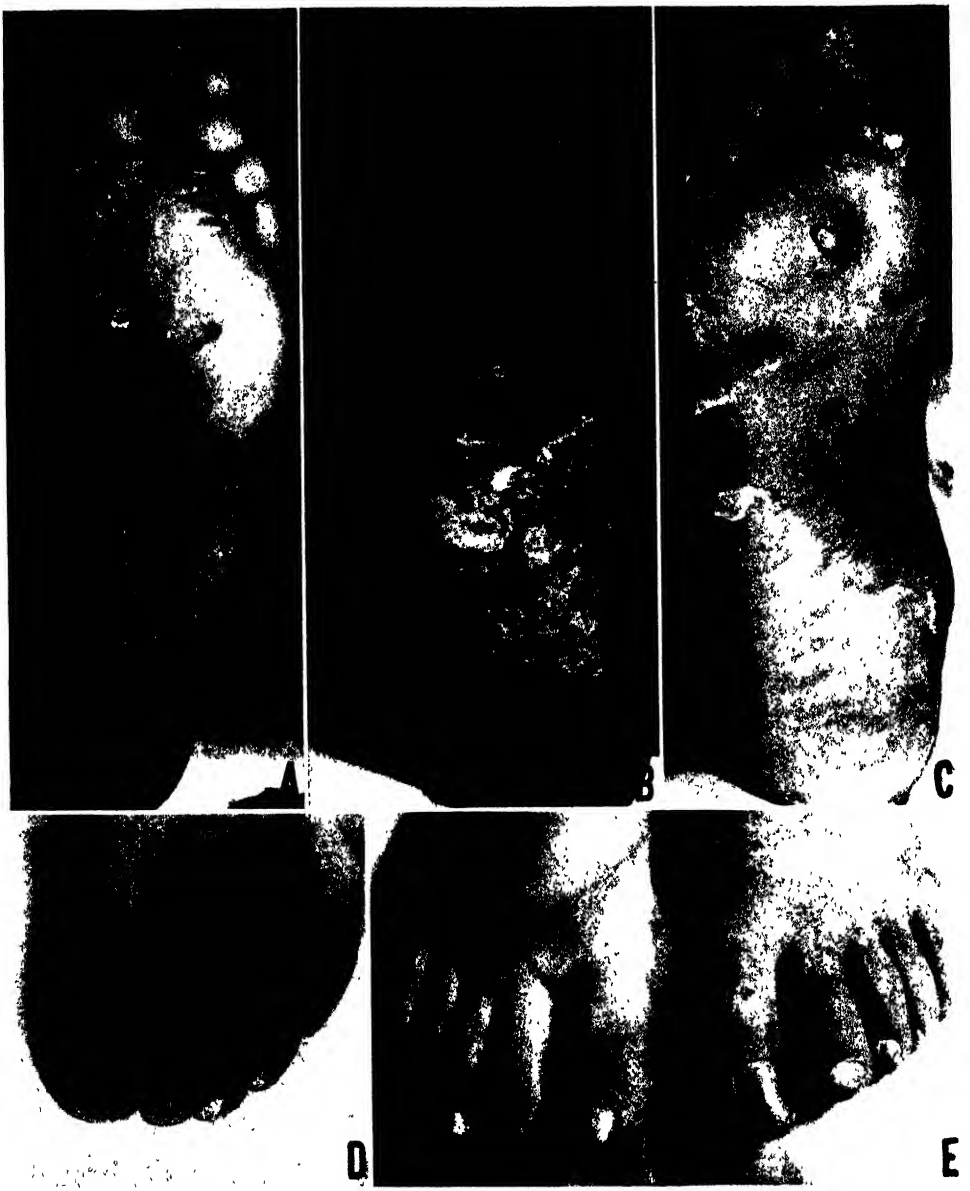

FIG. 32. Acute dermatophytosis. Culture yielded T. gypseum in each case. *A*, acute vesicopustular rash of two weeks' duration. *B*, severe pustulobullous infection somewhat improved after wet soaks in potassium permanganate solution. *C* shows that after the subsidence of inflammatory tinea pedis there are scaling of the sole and interdigital maceration. Treatment should be continued in order to eradicate the disease. *D*, superficial infection of the nail (leukonychia trichophytica) and vesicopustules, with fungi in both sites. *E*, interdigital maceration and scaling and superficial involvement of several toenails.

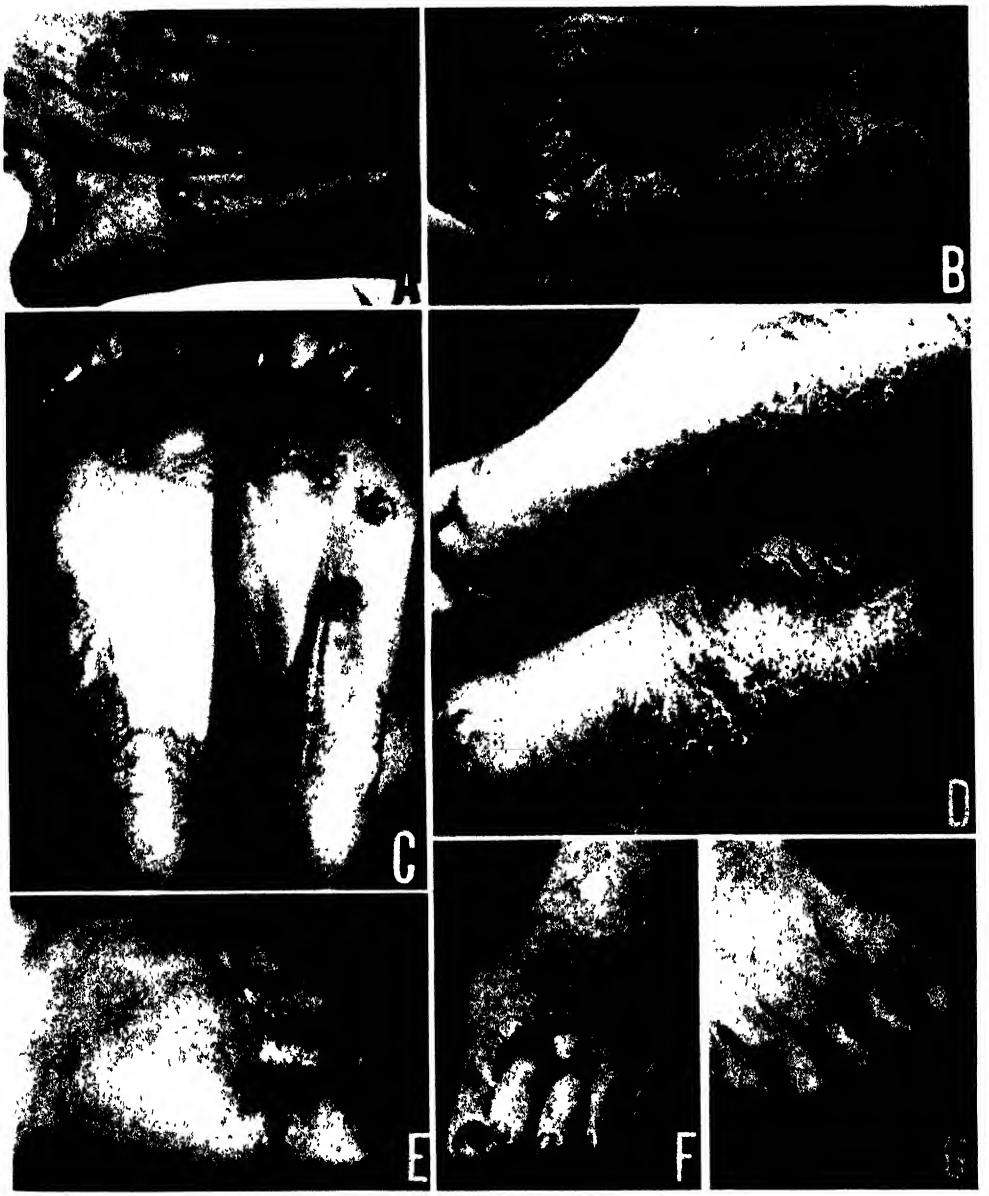

FIG. 33. Acute dermatophytosis (T. gypseum). *A*, maceration on the interdigital webs of the feet and vesicular rash on the sole and hands (no fungi discovered), considered a good example of dermatophytid. *B*, *C* and *D*, erythematous squamous eruptions suggestive of psoriasis. *E*, vesicular and exudative areas on the under surface of the toes, with sterile vesicles on the sole. *F*, secondary dermatitis following use of a strong ointment. In *G* the toes are swollen, red, vesicular and scaly. (*Courtesy of Royal Montgomery.*)

Because of mismanagement, a low state of resistance or a virulent strain of organism, the condition may spread from the feet to involve contiguous areas, which are sometimes of wide extent. The eruption is erythematous and vesicular in patches and is fairly well demarcated from normal skin. The folds and intertriginous areas are most vulnerable, and the infection may spread to any or all of the following sites: the upper parts of the thighs, the perianal region, the umbilicus, the axillae and the inframammary regions. There are a few instances of primary involvement of the hands and of other parts of the body. In instances of acute inflammation, secondary pyogenic invasion of the tissues is common. At times the pyogenic element overshadows the characteristics of fungous disease. If the process becomes frankly pyogenic and spreads, the disease may have changed to infectious eczematoid dermatitis. Many clinicians believe that eczematous eruptions on the hands or elsewhere may be originally of fungous origin but persist owing to coincidental sensitizations or secondary pyogenic involvement. It is our opinion that fungous disease predisposes to contact sensitivity, so that a patient who ordinarily is not reactive to soap, dyes, salicylic acid, etc., may develop an inflammatory response to these or to many other drugs or chemicals, and that this superadded insult to the skin is often important in accounting for the lack of response of the disorder to therapy.

B. Involvement of the nails. As part of the process, the nails, particularly of the toes, are not uncommonly affected. In fact nail tissue may be the first to be involved. The infection with T. gypseum may be superficial, merely causing a white patch on the surface or in the substance of the affected nail (leukonychia trichophytica). At other times there may be a more inflammatory and destructive involvement, in which case the nail becomes yellowish, opaque, lusterless and finally friable. The nail bed may become slightly erythematous, and separation of the nail from its bed may occur, this process usually beginning distally. Subungual hyperkeratosis and uneven dystrophic changes in the nail are frequent. Paronychia is rare. When destruction occurs, the process is fairly rapid, although there are rarely more than three nails affected. Subjective symptoms are usually mild, but pain may be severe.

(2) *Chronic type* (*Trichophyton purpureum*).—In this form there is practically never vesiculation or acute reaction. The interdigital webs alone may harbor the organism, in which case the appearance does not differ noticeably from that of the latent form described in the section on the inflammatory type, although the duration is often considerably longer.

Further characteristics of the infection may be described from the standpoint of the sites of involvement.

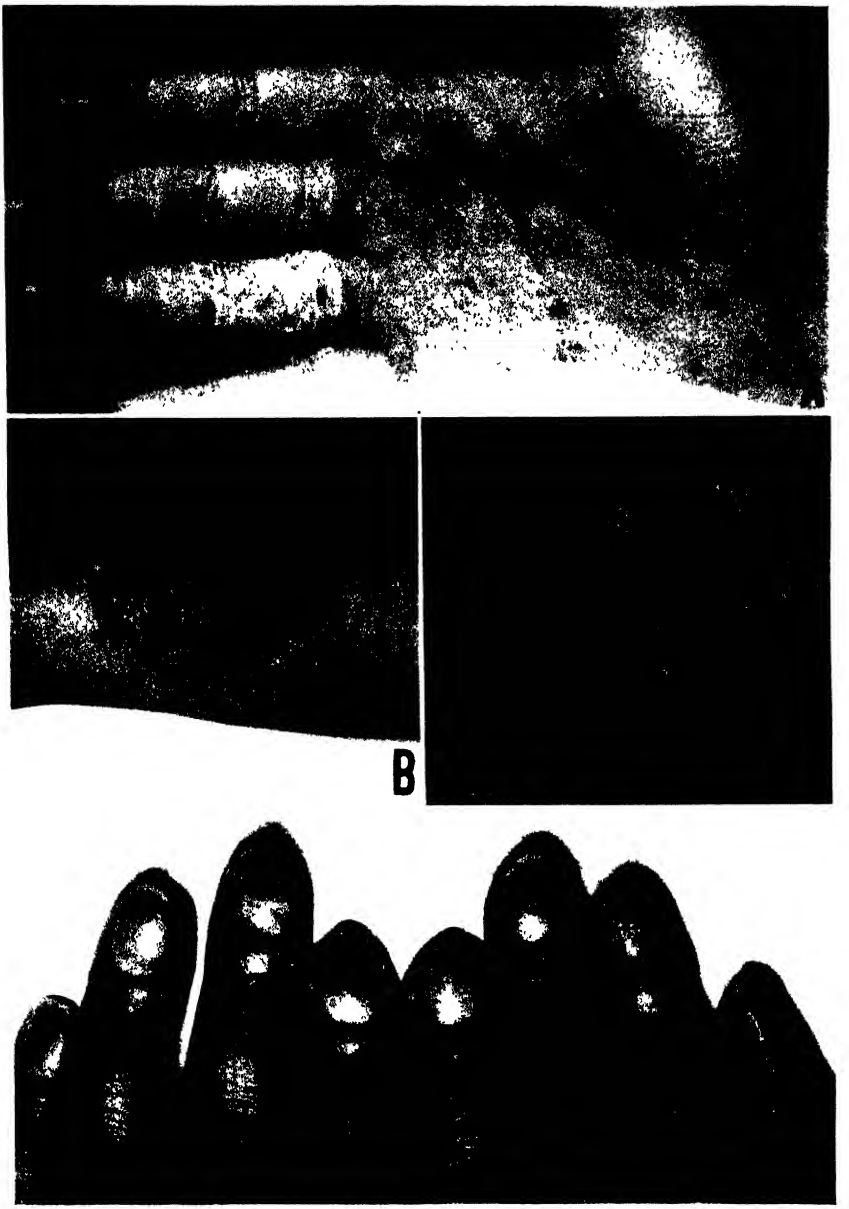

FIG. 34. Acute dermatophytosis of the hands. There may be a focus on the webs of the feet, on the soles or elsewhere, or the infection may be primary. With secondary infection, dissemination may take place externally or through the medium of the blood stream. *A*, acute vesicular rash secondary to lesions on the feet. While this might be classed as dermatophytid, T. gypseum was isolated from the lesions. *B*, primary erythematous vesicular infection of short duration from which T. gypseum was isolated. There were no lesions on the feet. *C*, well defined subacute rash of the hand, with part of an eruption also on the feet, elbow and face, of one year's duration. *D*, early involvement of nails, showing destruction and separation at the base. The violence of the process produced a spontaneous cure, and new nails were normal.

A. Involvement of the hands and feet. The appearance of the eruption on the feet and on the hands appears to be peculiar to T. purpureum. Lesions of the feet may occur on the soles, the sides, the dorsa, the toes or the nails. The plantar surface is a common site. When the hands are involved, the palms, the dorsa, the fingers or the nails may be affected. Itching is frequent.

The entire sole is frequently involved, but the infection may be localized to a small area around the heel or on the ball of the foot. When the sole is involved, the infection usually extends to the sides of the foot and about

TABLE 17.—Location of Infection Caused by T. Purpureum in 240 Patients

	Skin	Nails	Skin and Nails	Follicles	Total Infections
Feet	180	99	72		207
Hands	44	62	21		90
Trunk, arms and legs	27			1	27
Inguinal region	35				35
Trunk (gyrate)	5				5
Face	3			2	3

the heel. The infected skin is dull red and slightly thickened or indurated. The scaling, which is constant, is usually fine and thin (branny), in contrast to the large flaky scale found in psoriasis or in some types of dermatophytosis. The absence of visible vesiculation in the infected area is a persistent feature. Hopkins and his group reported that in many of the patients with T. purpureum infections studied at Fort Benning, 1942–45, the eruption was acute, severe and extensively vesicular. This is at variance with our (civilian) experience and may be explained partially by the climate and conditions under which the soldiers were living and the probability that these young men were experiencing their initial attack. There is usually a sharply marginated border along the outside of the foot, between the infected skin and the normal skin on the dorsum.

Small irregular infiltrated erythematous and scaly patches may be found on the dorsum of the foot and on the toes. The degree of erythema may vary within a single patch. There is no tendency to central clearing.

The infection of the under surface of the toes and of the interdigital webs is clinically similar to the infection of the sole, sometimes with the addition of a certain amount of maceration. When the entire area about the toe is infected, the skin appears thickened and dry. Painful fissuring may occur about the joints.

The eruption on the hands is similar to that on the feet. The entire palm may exhibit the characteristic dull red color, with thickening and scaling.

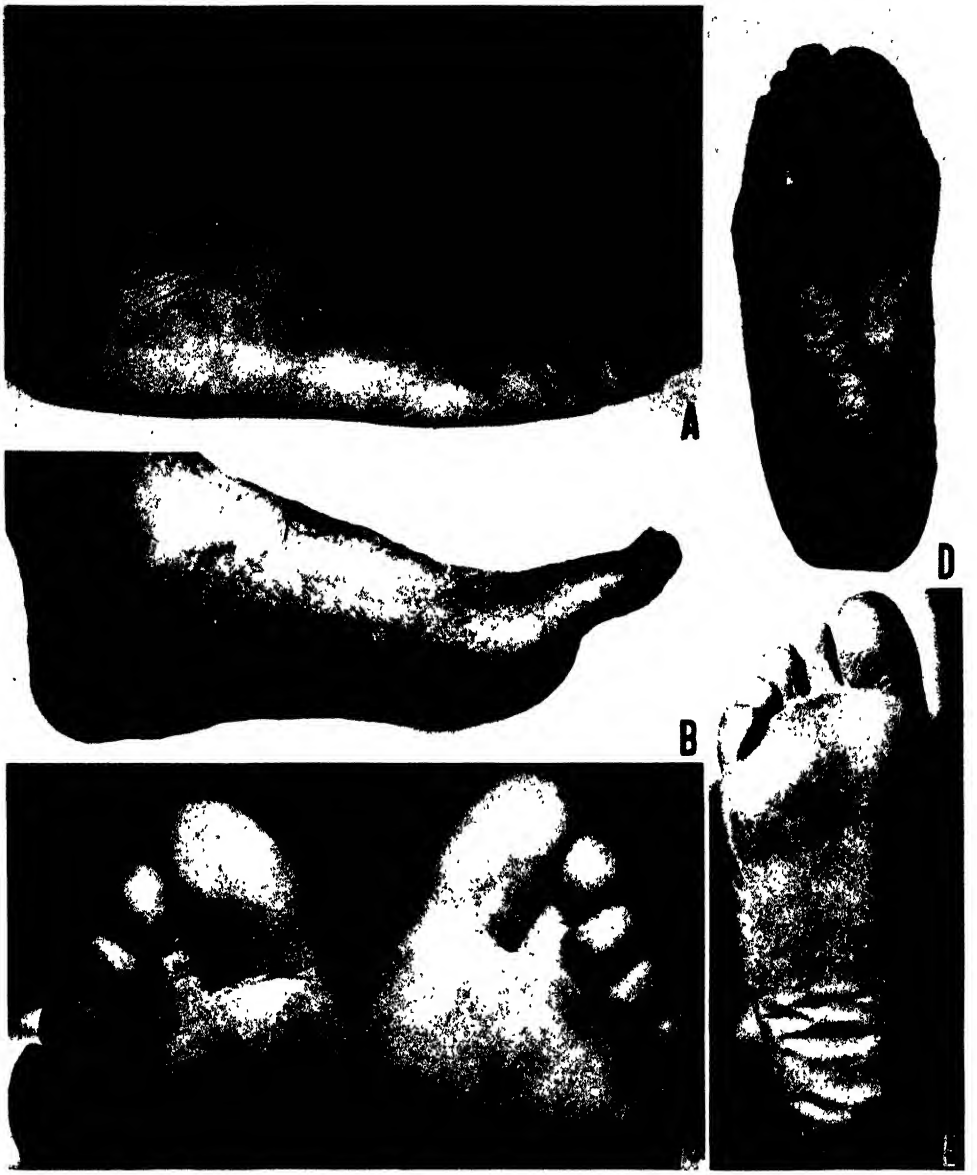

FIG. 35. Chronic dermatophytosis of the feet (T. purpureum). In *A* and *B*, the affected skin on the dorsa and insteps of the feet shows a dull red, scaly, slightly edematous, well defined rash. *C*, scaling on the interdigital webs. *D*, marked hyperkeratosis in an untreated condition of long duration. In *E* the skin is diffusely thickened and scaly.

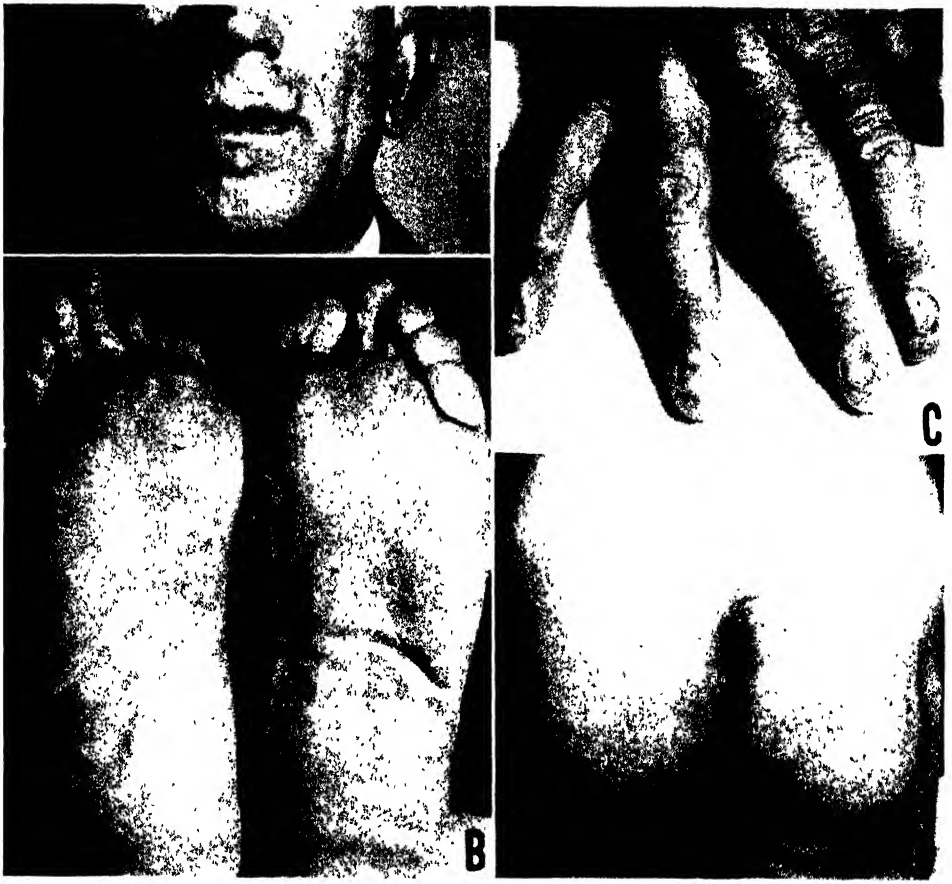

FIG. 36. Ringworm infection due to T. purpureum, showing multiple foci. *A*, follicular lesions on the upper lip. In *B* the soles are dull red, thickened and scaly. *C*, dystrophic fingernails. *D*, ill-defined scaly lesions across the buttocks. The organism was demonstrated by culture of material from all the sites.

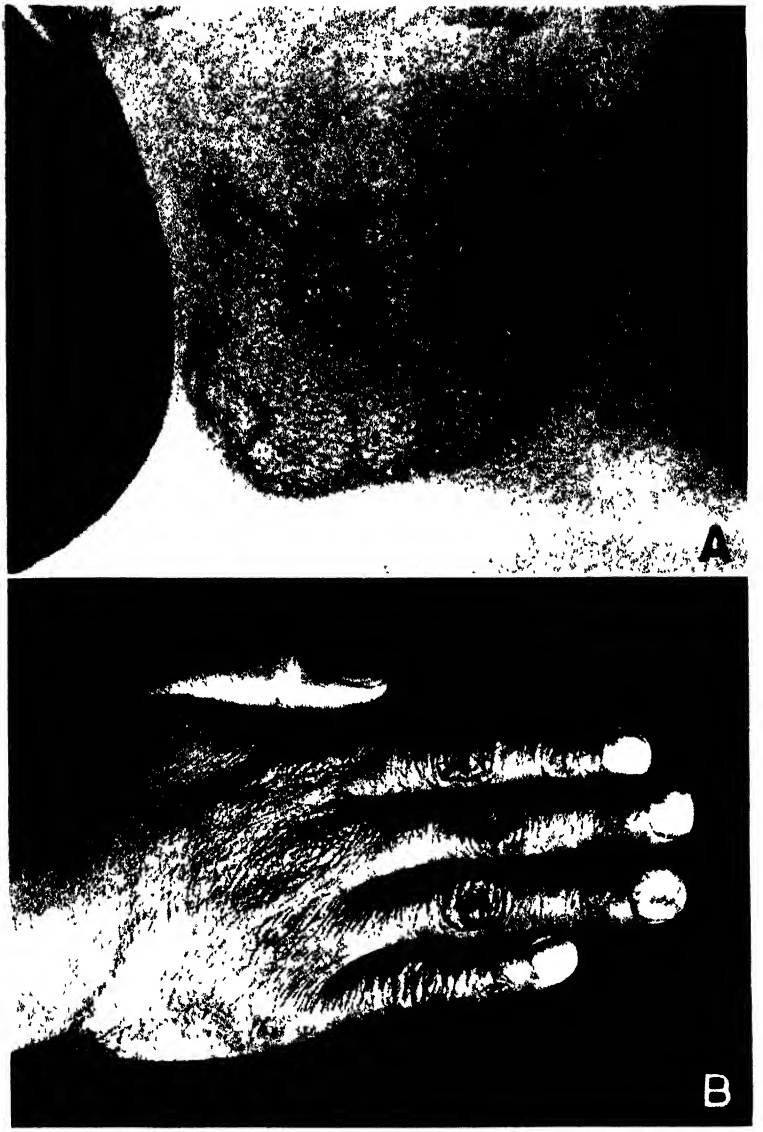

FIG. 37. Infection due to T. purpureum. *A*, thickened, dry, scaly plaque on back of neck. *B*, solidly involved area over fingers and back of hand, with sharply marginated border; the ring finger nail is yellow, opaque, thickened and spooned.

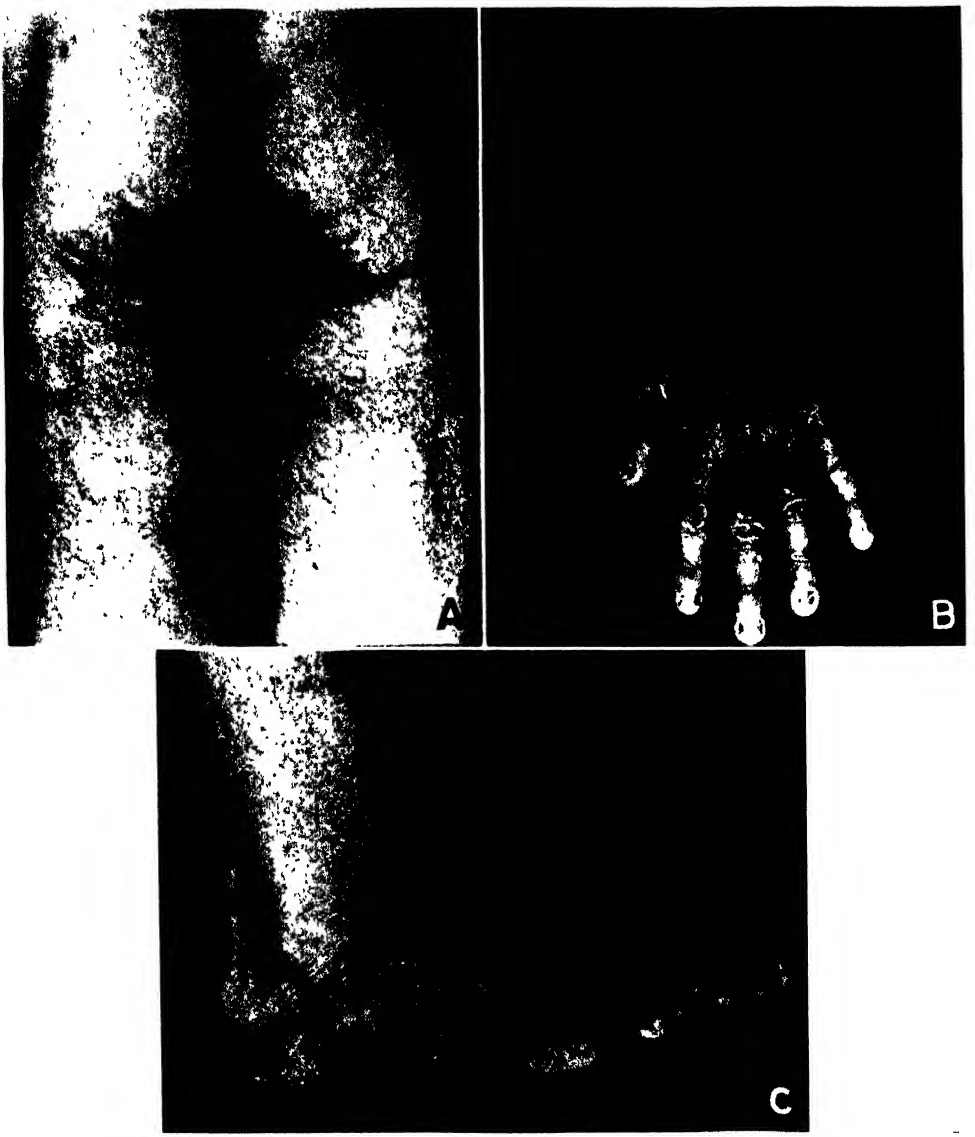

FIG. 38. Trichophyton purpureum infection involving the foot, hand, buttocks and thigh. Fungi could be isolated from all lesions without difficulty.

Friction and frequent washing in all probability make the scaling less apparent than that on the soles. The erythema may be slight and the condition thus be considered a callus. Isolated irregular patches may be present about the dorsum of the hand and on the fingers, as is the case with the feet. Frequently the skin of an entire finger is involved. Redness of the skin with or without scaling may be noted over the joints of the hands. Fissuring in affected patches about the joints is a fairly constant feature. The absence of vesiculation, except in rare instances, and the presence of severe itching are again notable. On several occasions, when the palm was involved, we observed a marked decrease in the amount of sweat.

B. Involvement of the nails. Nails infected with any pathogenic fungus except M. albicans are usually opaque, lusterless, friable and yellowish. Varying degrees of dystrophy, as evidenced by irregularities of the nail plate, separation of the nail and subungual hyperkeratosis, are frequently present.

Nails infected with T. purpureum sometimes have certain features peculiar to this organism and not always shared by nails infected by other fungi. Unlike ungual infections caused by T. gypseum, the condition due to T. purpureum does not often concomitantly involve the interdigital webs of the toes. Furthermore, a superficial location of the infection on the surface of the nail is frequent with T. gypseum but practically unknown with T. purpureum. The duration of the infection is shorter and the progress of the infection is faster with T. gypseum.

The onset and progress of the ungual infection due to T. purpureum is slow and insidious. When the condition is first observed, one or more nails may be involved. Frequently the patient who has applied for treatment of infected fingernails may unknowingly have involvement of the toenails and even of the feet. There is little reaction in the subungual and paronychial tissues. We have not observed paronychia in our cases. (Compare infections due to T. gypseum or to M. albicans.)

The infection usually begins under the free border or along the lateral margins of the nail plate. We have observed a single case in which the infection started in the proximal portion of the nail. Yellow or white vertical streaks may appear in the nail, seeming to result from separation of the nail plate from its bed. These streaks gradually widen; the nail separates more and more and débris accumulates. There may be gradual involvement of the distal end of the nail, without the usual formation of streaks. Meanwhile the nail itself becomes thinned, owing to gradual invasion of the fungus. The nail becomes brittle, and the distal portion may be broken or worn off, leaving only the proximal part. Sometimes the entire nail plate is lost, leaving the nail bed covered with scales and débris.

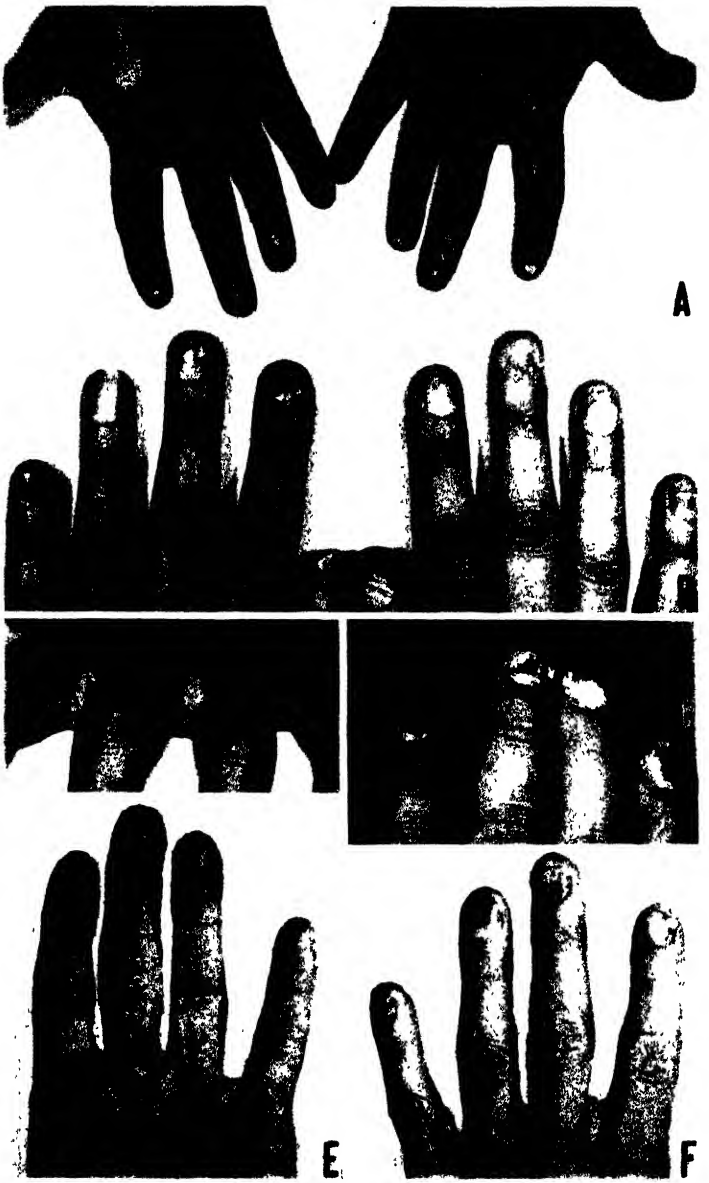

FIG. 39. Chronic dermatophytosis of the hands and fingernails (T. purpureum). *A*, condition which involved all the fingernails and toenails. Dull red, scaly and infiltrated lesions may be seen on the backs of the fingers and hands. *B*, fingernails showing different degrees of destruction. The infection usually progresses slowly. (*Courtesy of Royal Montgomery.*) *C*, dry intertrigo of the finger webs. *D*, advanced and early manifestations. The nails of the ring and little fingers show friable opaque yellow areas at the proximal portions, where the infection was introduced by a nail file. *E* and *F* show fingers and fingernails of a school teacher who had had the infection for 17 years. The moth-eaten appearance of the nails and the thickened scaly skin are well shown.

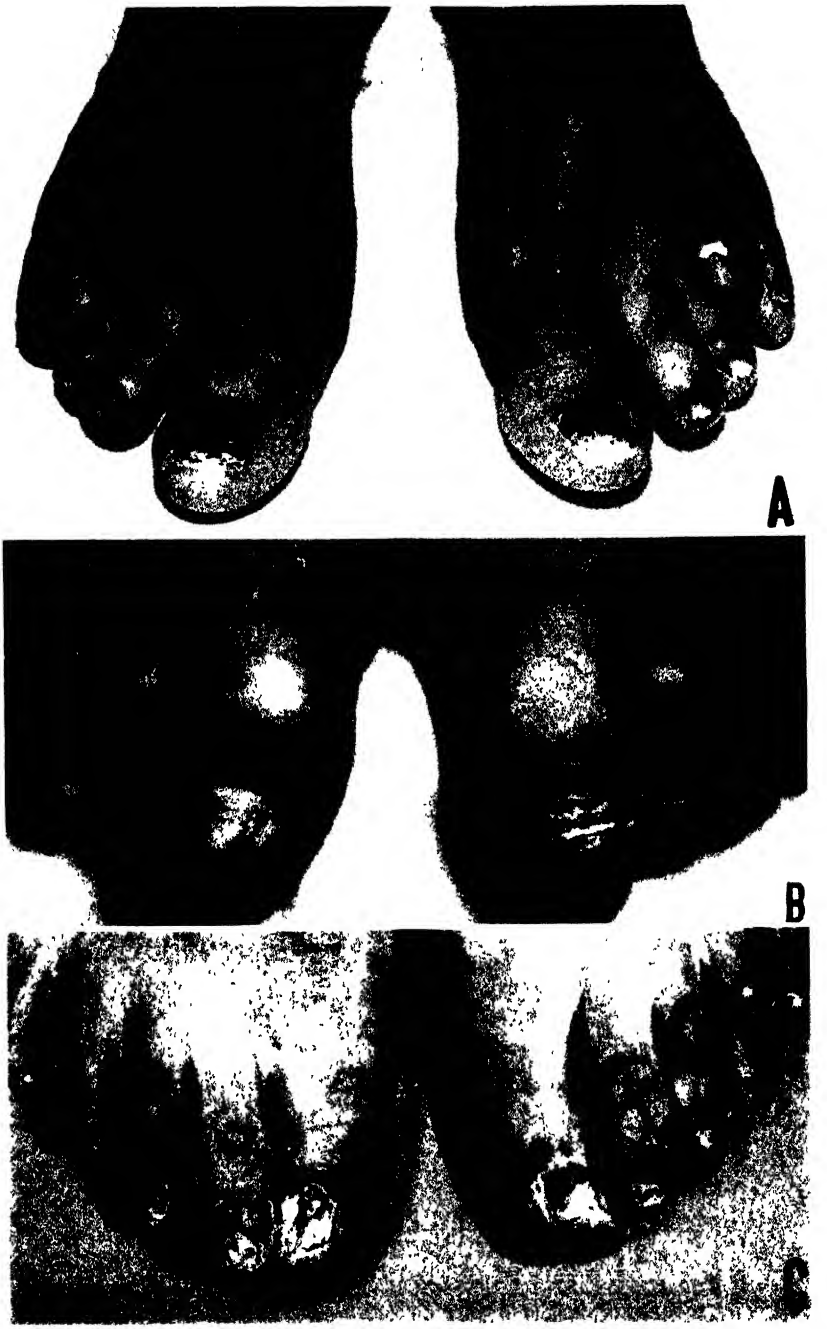

FIG. 40. Chronic dermatophytosis (onychomycosis) due to T. purpureum. *A*, involvement of all the toenails. In *B* the left great toenail has been pared down to show the depth of involvement. The right great toenail is yellowish, opaque and friable. *C*, marked crumbling of the toenails with neglected involvement.

Only once have we been able to isolate T. purpureum from the surface of a nail obviously infected by fungi and never from a nail with no clinical evidence of fungous involvement. In connection with these observations we wish to point out that scrapings from the surface of an infected nail frequently contained the ordinary saprophytes but that when scrapings from the deeper portions of the nail were planted on agar slants, T. purpureum in pure culture resulted. For this reason cultures of infected nails should be taken from different depths in the nail substance. Unless the deeper portions are examined (and even when they are) a number of scrapings may be required before the organism can be cultured.

Infection of a fingernail should always invite examination of the toenails, since the two sites are frequently simultaneously affected. In onychomycosis caused by T. gypseum and also when T. purpureum is the pathogen the toenails are involved more frequently than the fingernails in the ratio of 11:1.

c. Involvement of other regions. It should be noted that lesions attributable to T. purpureum may appear on the glabrous skin, on the upper parts of the thighs and in the inguinal and perianal regions, and occasionally the organism produces infection of the hair follicles. Peculiarities of the infection in these locations have been considered in the sections on tinea sycosis (pp. 75 ff.), tinea glabrosa (pp. 78 ff.) and tinea cruris (pp. 93 ff.). Thompson and others have offered experimental proof that thromboangiitis obliterans is caused by infection spreading from the feet and due to T. purpureum. Reiss and Graham failed to reproduce the disease in animals and at this time the question of causal relationship must be considered not settled.

(f) Dermatophytid.—This subject was briefly considered in the section on tinea capitis (pp. 47 ff.). The term dermatophytid is probably better than trichophytid, since allergic rashes due to Microsporum may be clinically indistinguishable from those due to Trichophyton. Guth, Bloch, W. Jadassohn, Peck and others have contributed to our knowledge of these rashes. It has been stressed by Bloch, Jadassohn and their school that allergy or an acquired specific sensitization is an invariable accompaniment of the rash. The eruption was at first thought to follow deep infection only, being considered due to dissemination of the products of fungi through the blood stream. Williams was the first to show that secondary eruptions may follow infection of the interdigital webs, and he later also found that macerated tissue in the groin may act in a similar way as the focus for a secondary rash at a remote point. The suggestion that nails may act in like manner as a focus for direct dissemination of the products of fungi through the blood stream has not been confirmed. It is notable

FIG. 41. Dermatophytid, secondary to tinea pedis. Trichophyton gypseum was cultured from the feet of all four patients. *A*, typical appearance, with severe vesicopustular lesions. The palms and sides of the fingers are the sites of election. No fungi were demonstrated in these lesions. *B*, acute vesicopustules with beginning eczematization. *C*, keratolysis exfoliativa, showing fine branny scaling. *D*, chronic edema of the ankle and leg of a patient who had repeated attacks of acute lymphangitis; both fungi and streptococci were isolated from the interdigital webs.

also that with the dermatophytid described by Williams there was a tendency to a localized rash, the sides of the fingers and the palms usually being the sites. The reason for this localization is not known. The terminal circulation of the hands, traumatic factors, contact with fungi producing local sensitization and sensitization to light have been considered. It is not by any means a unique experience in dermatology to be unable to explain localization of a disease process. No one has satisfactorily explained the frequent involvement of the knees and elbows in psoriasis. In the classic dermatophytid following a deep infection of hair follicles, the trunk was usually involved. In this latter instance the character of the rash varied considerably. Follicular localization of lichenoid papules was common, but eruptions simulating erythema toxicum were also observed. In the type described by Williams, the lesions are essentially vesicular, being similar in appearance to dyshidrosis, although the contents frequently become purulent. Constitutional symptoms, often associated with dermatophytids secondary to kerion, are not commonly part of the syndrome which includes a rash secondary to tinea pedis.

The term dermatophytid (or trichophytid) appears to have been considerably overworked in this country. It is used by many without any tangible evidence of proof to account for the erythematous, vesicular and eczematous eruptions which so commonly affect the hands. We believe that a diagnosis of dermatophytid should be arrived at only after careful observation and study. There are definite criteria which must be fulfilled before this diagnosis is acceptable. Peck has laid down theoretically sound rules. His dictum that a positive blood culture is essential is perhaps too drastic. The following conditions for the diagnosis of dermatophytid, however, are minimal and also obligatory.

1. There must be a demonstrable focus, and this focus must contain pathogenic fungi. On the feet, in the majority of instances, the causative fungus is T. gypseum. We have never observed dermatophytid with T. purpureum.

2. The secondary rash may be due to irritation of the primary focus by treatment or to a spontaneous inflammatory change.

3. The intracutaneous test with trichophytin reveals a positive reaction at the test site.

4. Fungi are usually not found in the lesions of dermatophytid.

5. The rash disappears spontaneously when the focus has been eradicated. The only exceptions occur when there are secondary eczematous changes and the rash continues because of sensitivity to other substances or because of the action of primary irritants.

In all cases, even if the appearance of the rash and the results of the

investigation point to dermatophytid, possible sensitization from external contacts should be considered, and patch testing with suspected substances is always in order.

The same type of vesicular dermatophytid which appears on the hands may also be found on the feet, particularly on the soles. Here, as on the hands, examination for fungi may yield negative findings.

The condition known as keratolysis exfoliativa was studied by MacKee and Lewis, who considered that it is often a form of dermatophytid. They found that it frequently occurred in patients who had an active mycosis of the feet and that vesicular dermatophytids were commonly present. In keratolysis exfoliativa the lesions consist of superficial scaly macules, which may coalesce and are localized to the palms and/or soles. The lesions at first are unruptured empty vesicles. The scale is as thin as cigaret paper. When it is broken, collarets are formed at the edges. Only a few lesions may develop, or most of the skin on the palms and soles may be affected. The almost constant presence of the mosaic fungus is considered significant.

Another type of dermatophytid occurring on the legs has been described as erysipelas-like. It appears to be proved that in some of the reported cases secondary allergic lesions arose from a focus on the interdigital webs of the feet. In other cases, little proof was offered that the lesions were not in reality of streptococcic origin. In several instances of eruptions of this character, with localized erythema and swelling and sometimes with fever and prostration, fungi were demonstrated in scrapings from the feet. The trichophytin test, however, did not elicit a positive reaction in every case, even when a site near the lesion was tested. Furthermore, in a number of instances bacteriologic studies revealed the presence of streptococci. Further study appears to be necessary to prove beyond doubt that in all or in most of these cases the condition is entirely due to the dissemination of fungi from the focus on the feet.

Moreover, it must not be forgotten that many lesions at points remote from the initial infection are due to external dissemination of fungi. These lesions are not dermatophytids and certainly should not be classed as such.

(g) Histology.—The findings vary according to the infecting microorganism.

(*1*) *Acute infection.*—The changes in acute dermatophytosis are similar to those observed in acute eczematous eruptions. The stratum corneum shows some parakeratosis. Small vesicles are to be seen below this layer. The intensity of the process determines the degree and extent of vascular dilatation, of edema and of round cell infiltration in the upper cutis. In other words, there is a superficial exudative inflammatory process with some epidermal (eczematous) changes.

(2) *Chronic infection.*—In the chronic form there is a simple inflammatory process in the upper part of the cutis. The vessels are slightly dilated; cellular elements are of the small round type and are sparse. There is moderate interstitial edema. The epidermis is slightly acanthotic. At times there is marked hyperkeratosis. The basal cell margin is intact. There is no intercellular edema, spongiosis or vesicle formation; occasional areas of parakeratosis are noted.

(h) DIFFERENTIAL DIAGNOSIS.—As in the diagnosis of other forms of mycotic infection, laboratory methods should be employed for every patient suspected of having this fungous disease. The information to be obtained by such studies is frequently the only means of definitely establishing the diagnosis.

(1) *Interdigital lesions.*—If the infection is present on the interdigital webs of the feet alone, it may be impossible to determine the species of infecting micro-organism by clinical observation. If all the webs are affected, infection with M. albicans is probable. The bright red base and overhanging collaret of skin suggest moniliasis. Intertrigo caused by T. purpureum or by T. gypseum may be indistinguishable. There are a number of instances of failure to demonstrate a pathogenic fungus. In some of these cases certain bacteria, especially strains of hemolytic streptococci, have come under suspicion without decision.

Scaling between the toes due to the injudicious use of strong chemicals may lead the physician astray. Several instances of this character have come under our observation. The lack of laboratory confirmation and healing under bland applications tend to rule out tinea pedis. Maceration of the interdigital webs without evidence of inflammation may be caused by increased perspiration or by lack of drying after the bath. Such tissue is vulnerable to pathogenic fungi and to bacteria.

Syphilis may produce lesions difficult to distinguish from those of acute tinea pedis. The bright red, fleshy, exudative character should make one suspicious, and examination for condylomas or other evidence of the infection will be fruitful.

Soft corns are not uncommon and may be found in association with a fungous infection. They are, however, caused not by a fungus but by pressure of ill-fitting shoes. When they are present at the base of the web they may on superficial examination suggest tinea pedis.

(2) *Acute inflammatory tinea pedis.*—Acute tinea of the feet, caused most commonly by T. gypseum, is usually accompanied by interdigital maceration. It should be remembered, however, that inflammation of the foot and tinea of the webs may be unrelated disorders. In most cases of inflammatory tinea the reaction to the trichophytin test is positive.

At times patients are seen who present soggy, thickened, honey-combed soles, most involved over points of pressure. The odor is that of dirty feet. Although this condition is almost invariably attributed to fungous infection, the results of culture are usually negative. It is our opinion that hyperhidrosis plus bacterial invasion is responsible.

Dermatitis venenata due to sensitivity to shoe leather, to the dye in stockings, to foot powder and to corn cures and the like should be considered when the inflammatory disorder is first limited to the region of the contacted substance. Once this dermatitis is established, secondary eczematous changes may quickly occur, further confusing the picture. The lack of other evidence of fungous disease, the negative findings on mycologic examination, the results of patch testing and cure when the offending article is eliminated from the environment of the patient aid in establishing the correct diagnosis.

When part of a widespread eczematous condition, whether due to contact or to some other cause, the involvement of the feet or ankles may mislead the unwary physician. He may consider the whole eruption mycotic because the feet are involved. In these cases, if the trichophytin reaction is negative, the diagnosis of tinea may be excluded.

The disease known as pustular psoriasis frequently presents a confusing picture. The lesions appear in groups of small, thick-walled pustules. The arch and the heel are the commonest locations on the foot, but lesions may develop elsewhere. Frequently the hands are concomitantly involved. The lesions are usually sterile. Barber, Andrews, Hopkins and others have observed that in such cases cure has resulted from the removal of foci of infection. The resemblance to tinea pedis may be striking, but lack of interdigital infection, localization, resistance to therapy and lack of mycologic confirmation should be sufficient to indicate the correct diagnosis.

With acrodermatitis perstans or dermatitis repens, which are similar, if not identical, disorders, the initial lesion is usually paronychia. From this arises an undermining pustular eruption, which spreads on one digit and may finally involve large sheets of skin. If the condition is untreated, an exudative eczematous process ultimately develops.

Streptococcic infections have been credited by Mitchell with causing lesions on the feet which resemble those due to fungi.

Orbicular eczema is superficial, does not show a tendency to central clearing and does not respond to the usual fungicides. Results of all laboratory examinations are negative.

(3) *Chronic types of infection.*

A. Psoriasis. So-called aberrant types of psoriasis are usually due to T. purpureum. While the diagnosis can be made with certainty only from

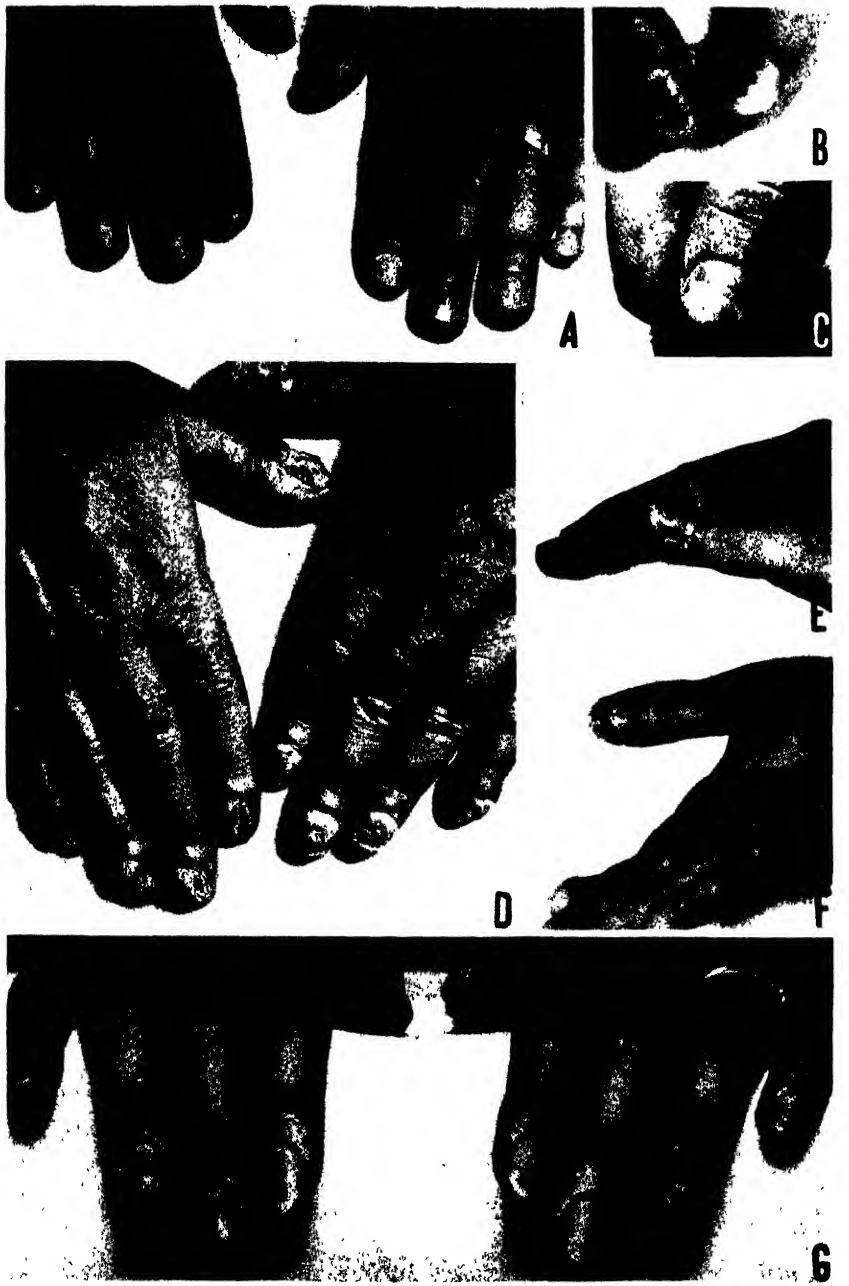

FIG. 42. Nonmycotic diseases simulating dermatophytosis. *A*, pitting of fingernails of a patient with psoriasis. *B*, congenital defect. *C*, onycholysis. *D*, severe dystrophic onychia with bulbous terminal phalanges. Typical psoriatic lesions were present elsewhere. *E* and *F*, acrodermatitis perstans (Hallopeau). *G*, pustular psoriasis.

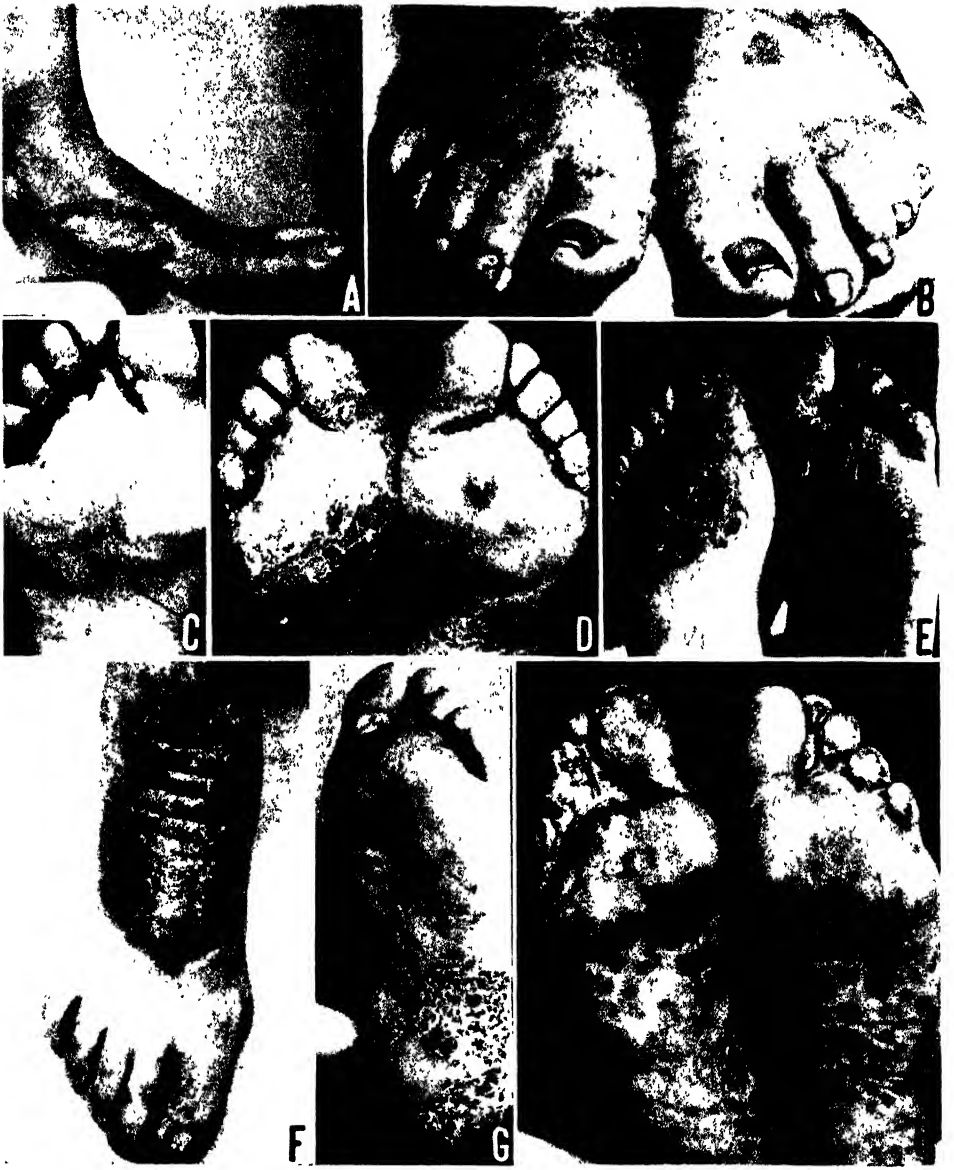

FIG. 43. Nonmycotic diseases to be differentiated from dermatophytosis. *A*, dermatitis venenata due to shoe leather. *B*, dyshidrosis, or pompholyx. *C*, *D*, *E* and *F*, psoriasis. *G*, pustular psoriasis. *H*, syphilis with maculopapular lesions on the soles and moist, eroded lesions on the webs and under surfaces of the toes. (*C to H, courtesy of Royal Montgomery*)

mycologic examinations (usually repeated several times), the lack of involvement of the scalp and the localization to areas not commonly the sites of psoriasis, such as the palms, the soles or the inner surfaces of the thighs, should make one suspicious. The presence of bleeding points after removal of the scale is not usual with the mycotic disorder. The histologic picture usually observed with psoriasis is absent in case of fungous infection. Pruritus, if severe, favors the diagnosis of dermatophytosis.

B. Neurodermatitis (atopic eczema). On close inspection the affected patch will be seen to be lichenified, with exaggerated cutaneous markings. Scratch marks may be noted, as with the fungous disease. Careful investigation of the history will elicit the fact that pruritus and scratching by the patient preceded the rash. There may be a history of allergy to foods or to inhalants or a tendency to another allergic disorder, such as hay fever or asthma.

(*4*) *Onychomycosis.*

A. Infection with Monilia albicans. Chronic paronychia is practically constant. The edges of the nail become yellow and eroded or develop a dark stripe, but the nail substance is frequently firm and translucent. Uneven ridges and grooves are probably due to interference with nutrition. Most of these signs are not seen in nails infected with T. gypseum or T. purpureum.

—B. Psoriasis. Pitting of the nails is frequent. Ridges and grooves sometimes

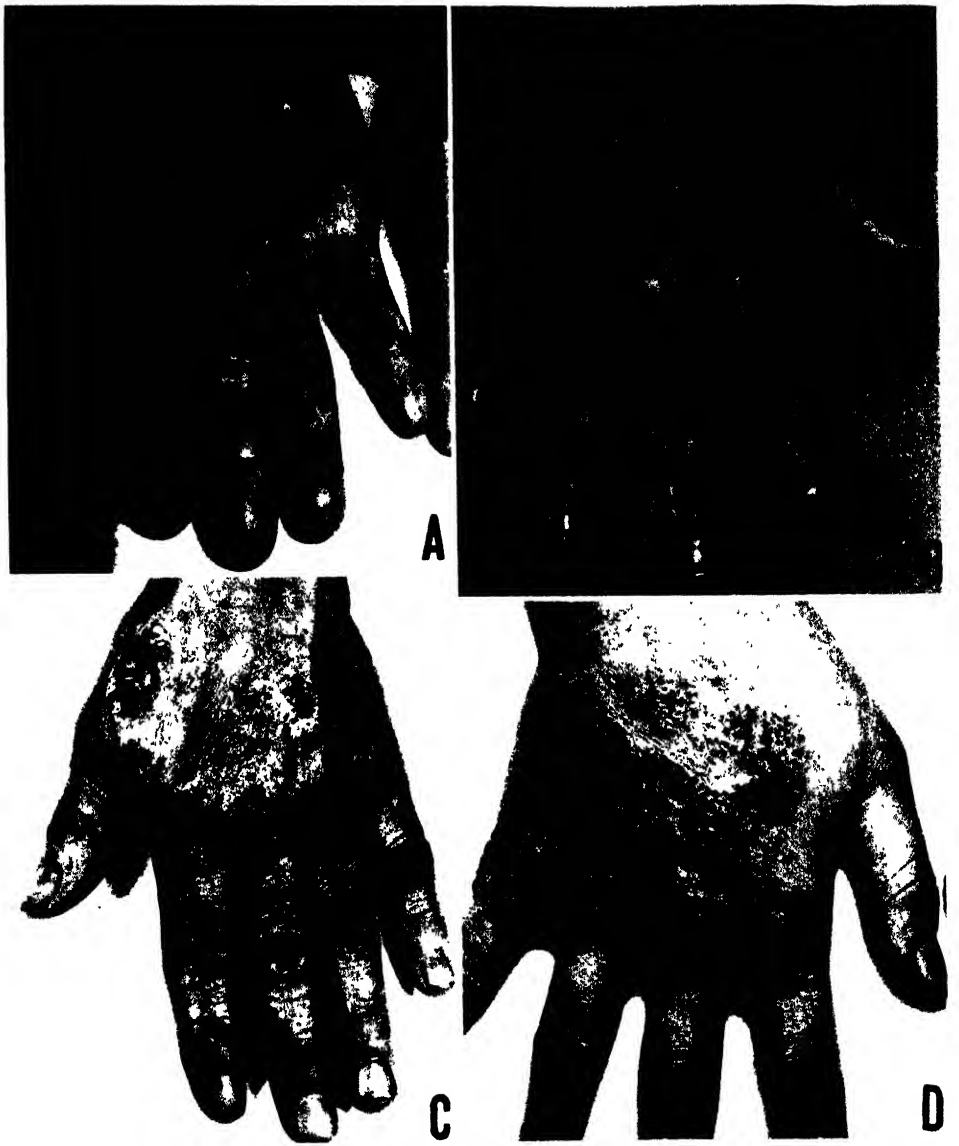

FIG. 44. Nonmycotic rashes simulating dermatophytosis. *A*, dyshidrosis, or pompholyx. *B*, erythema toxicum. *C*, contact eczema. *D*, so-called parasitic, or nummular, eczema.

changes in the substance of the nail is usually due to M. albicans. In the invasive type of filamentous infection, the cardinal symptoms of yellowness, friability and opacity of the nail and the negative sign of lack of paronychia will usually point to the correct diagnosis. The white specks or patches frequently seen on the edges of toenails are due to the presence of T. gypseum.

(5) *Dermatophytid-like eruptions.*—Toxic eruptions simulating dermatophytid may result from sensitivity to certain drugs. The absence of signs of a focus of tinea, the lack of an inflammatory focus on the feet and the history of ingestion of a drug point to the correct diagnosis. When a vesicular eruption is present on the hands, particularly on the fingers and palms, the diagnosis of dermatophytid is commonly given even without corroboration. In the majority of cases, however, such a condition is not of fungous origin. The criteria for the diagnosis of dermatophytid have already been detailed; it is at least necessary to find an active fungous focus and to observe a positive reaction to the trichophytin test. The diagnosis of dyshidrosis or pompholyx is made by excluding dermatophytid and dermatitis venenata. The former disorder has been discussed; in diagnosing the latter, one is helped by the absence of an active fungous focus and of a reaction to trichophytin, but their presence does not exclude the condition. An accurate history of contact with a possible sensitizing agent, particularly if the initial exposure was fairly recent, may point to the correct diagnosis. When secondary eczematous changes result from trauma or misdirected therapy, an additional factor or factors may make a definite diagnosis impossible. At present, unfortunately, a large number of patients with such lesions present themselves for treatment; they constitute a rather unsatisfactory group, in regard to both accurate diagnosis and therapeutic results. We believe that it is a mistake to classify all eczematous changes in the hands as dermatophytids. Another disorder previously mentioned, namely, pustular psoriasis, shows groups of deep-seated pustules. The sides of the fingers are rarely involved, the lesions are not evanescent, and response to therapy is poor.

(i) Prognosis.—This varies for involvement both of the skin and of the nails according to the infecting micro-organism, the allergic response in the patient, the factors predisposing to the infection and the duration and extent of the involvement. When T. gypseum is the causative fungus, the prognosis is hopeful. The infection may be severe, but cure may be expected. If T. purpureum is the offending micro-organism, cure is difficult and will probably take several months or even years. A vigorous reaction to the trichophytin test is a hopeful sign. As for the factors which predispose toward the disease, hyperhidrosis, unless it is controlled, may hinder a rapid response to therapy. If an underlying factor of ill health is uncor-

rected, the results of treatment may be disappointing. Everything else being equal, the longer the duration and the more numerous the areas of skin actually involved, the more difficult it is to eradicate the disease.

(j) TREATMENT OF SKIN.—Few dermatologic diseases have received more attention and space in scientific journals than dermatophytosis. The majority of the articles are clinical, and most are concerned with therapy or prophylaxis. It is unnecessary to mention the long list of proprietary drugs extensively advertised and sold to the public. In most textbooks as well, a long list of drugs and formulas is given. All this has led to confusion, and, as Osler has pointed out, the very multiplicity of remedies for a disease means that no one remedy has much value.

We agree with Mitchell that in an approach based on scientific logic one should first make an accurate diagnosis. Suppose that the disorder is localized to an interdigital web. We have mentioned that from the clinical signs one may not be able to differentiate between T. gypseum and T. purpureum as the causative fungus. A cultural diagnosis will assist one to determine the prognosis and the importance of treatment. Thus if T. purpureum is cultured, the interdigital maceration may be hard to eradicate, but treatment is essential if other areas are not to be subsequently infected. With T. gypseum, on the other hand, therapy is usually effective, but one need not be seriously disturbed if the treatment is not carried out faithfully.

The type of treatment should be indicated by the type of fungus present, cutaneous sensitization or lack of it and the clinical signs.

Our methods of treatment and their results leave much to be desired. Bechet stated an obvious truth when he declared that "the more experience one gains in the treatment of this obstinate dermatosis, the less faith one has in our present methods of treatment."

The various forms of therapy will be discussed according to the following subdivisions: (1) topical applications (keratolytics, fungicides and soothing agents); (2) physical agents (such as roentgen rays), and (3) biologic methods (injections of trichophytin, implantation of harmless saprophytes). Therapy of infections of the glabrous skin is discussed separately (see the section on tinea glabrosa, pp. 78 ff.). The treatment of dermatophytosis of the skin is taken up first; that of the nails next.

(*1*) *Topical applications.*—Some form of topical treatment is essential in all types of the disease. If involvement is localized to the interdigital webs of the feet or if it is widely distributed and T. purpureum is the infecting micro-organism, no other form of therapy need be considered.

The various medicaments to be applied to the surface of the skin include soothing agents, keratolytics and fungicides.

A. Soothing agents. These are required when acute inflammation is pres-

ent, whether on the hands, the feet or other parts. One should forget for the time being that the primary disease is mycotic. The safest application is a continuous wet dressing or soak, with use of Burow's solution (solution of aluminum acetate, 1:15); solution of boric acid (3 to 4 per cent) or solution of silver nitrate (0.125 to 0.25 per cent), particularly if there is an exuding surface, which indicates eczematization. Even when there are numerous unbroken vesicular lesions, wet dressings or soaks are best. Large pustules and blebs may be incised and all loose tissue clipped away. The same solutions or a solution of potassium permanganate (1:3,000) or of tannic acid (2 per cent) will be useful. If no secondary eczematization is present and if it is inconvenient or impossible to use wet dressings, the application of paints, lotions and powders may be considered. A 1 per cent aqueous solution of gentian violet (methylrosanilin) is soothing and, as Sutton pointed out, is not known to be a sensitizer. Damage to clothing may be controlled by careful handling. As substitutes, a 2 per cent solution of mercurochrome or an aqueous 1 per cent solution of brilliant green (malachite green) may be employed. The calamine shake lotion commonly used in the treatment of eczema and other cutaneous disorders may be used on the hands or body when an acute inflammatory disease is present. Purified talc to which 10 per cent each of zinc oxide and boric acid have been added is often gratefully accepted by swollen and acutely inflamed feet. When the acute vesicular character of the rash has passed, zinc oxide (20 per cent) in petrolatum may be followed by the sparse application of a tar (3 per cent juniper tar or 5 per cent solution of coal tar) in zinc oxide paste (10 to 20 per cent) or incorporated in boric acid ointment. If no irritation results, the use of stimulating remedies is in order.

B. Keratolytics. These are useful in peeling off the stratum corneum, which contains many fungi. By doing away with extraneous material they also prepare the way for the fungicides to act more effectively. The two drugs most commonly employed are salicylic acid and resorcinol. Most skins tolerate salicylic acid better. The strength of either drug depends on the site in which it is to be used and the character of the infection. Treatment between the toes is usually begun with a strength of 6 per cent. The same strength may be used on the soles. On the dorsa of the feet and on the hands a 2 per cent solution of salicylic acid should not be exceeded at first. If this is well tolerated, stronger concentrations may be used to promote more vigorous exfoliation. Satenstein stated that he used an alcoholic solution of salicylic acid in a strength of from 20 to 30 per cent.

These drugs are commonly employed with fungicides, although they may be used singly. The vehicle also may vary. According to some observers, drugs are more active in alcoholic or aqueous solutions than in grease. In

general, an alcoholic solution is probably superior to a salve when used on the webs of the toes or on the palms or soles. On other locations it is best to use a grease, since there is less irritation. Francis stated that he obtained satisfactory results with a mixture of camphor and phenol. He gave the following directions for making and using the preparation:

> Melt U.S.P. phenol and measure out 3 cc. into a mortar; weigh 3 Gm. of U.S.P. camphor, break into small pieces and add to the melted phenol. Rub until the entire mass is liquefied. Transfer into a vial with a stopper suitable for use as a dauber. Keep stoppered when not in use. Experiments indicate that the ingredients may be mixed in the proportion of 3 parts phenol and 1 part camphor.
>
> The mixture is nonirritating to the skin and may be painted between the toes several times a day, the small rubber stopper of the vial being used as a dauber. The sock may be replaced immediately without danger of corrosion. There is no discoloration of the clothing. Relief from itching is immediate. It should be pointed out, however, that the phenol-camphor preparation should not be applied to the wet skin, since water causes a breakdown of the preparation, with the result that it becomes caustic.

Confirmation is lacking that the combination of drugs is both safe and effective. Glenn and Hailey reported indifferent results in a series of 85 patients. We have seen the preparation misused and believe that unfortunate publicity through a lay periodical has resulted in considerable self-treatment with poor general results. Danger from local necrosis or from absorption makes the use of camphor-phenol undesirable.

In treatment of chronic infection of the feet due to T. purpureum, the use of the following paste was advocated by Glaze and by King:

Salicylic acid	3 oz.
Starch	3 dr.
Petrolatum	3 oz.

Only two applications, made on successive nights, are advised. A layer ⅛ in. (0.32 cm.) thick is placed on the entire affected area, covered with a bandage, left overnight and wiped off in the morning. No washing, however, is permitted. The result is the separation of the superficial cutaneous layers from the deeper parts, usually in a cast. There may be an acute inflammatory reaction. In several instances we have been impressed with the rapidity of response in patients who have used various other remedies without any improvement.

c. Fungicides. The exact mechanism of the lethal action of drugs on fungi is not fully explained. Some drugs apparently act as reducing agents. There is usually a certain degree of stimulation to the vascular supply. The degree of direct poisonous effect on the fungus is difficult to determine.

In choosing a fungicide, one may determine its activity in vitro and note its power to irritate human tissues and its effect after clinical trial. There have been several thorough investigations of various drugs. The

results of the work of Gould and Carter, Schamberg and Kolmer, Schamberg, Brown and Harkins, Kingery and Adkisson, and Emmons indicate that the fungicides to be discussed are active in the approximate concentrations named. Since these and other investigators based their results on the use of varied technics and different species of fungi, there are many discrepancies in the reports of the concentrations of drugs necessary to obtain the desired effect. There are, however, few actual differences of opinion.

1. Salicylic and benzoic acids were found to be only feebly fungistatic when tested separately by Schamberg and Kolmer, but Gould and Carter found that by combining and adding to culture mediums salicylic acid in the strength of 1:10,000 and benzoic acid 1:5,000, no growth resulted when the culture mediums were inoculated with six strains of common pathogenic fungi.

2. Iodine is strongly fungistatic (1:10,000) but not as strongly fungicidal (1:500). Schamberg, Brown and Harkins found iodine to be a powerful fungicide. Emmons, too, found it the most efficient fungicide, on the basis of its phenol coefficient. Others have confirmed these results.

3. Gentian violet, crystal violet and brilliant green restrained growth of fungi but were found to be less active as fungicides than as bactericides. Loos found brilliant green to be a most effective substance.

4. Mercurial products were effective both as fungistatic and as fungicidal agents.

5. Thymol, oil of cinnamon and oil of cloves were active in vitro.

6. Chlorine (sodium hypochlorite) was found by Emmons to be almost as effective a fungicide as iodine.

That complete reliance cannot be placed on laboratory tests is indicated by the poor results recorded for sulfur and chrysarobin. It is well known from clinical experience that both these drugs are valuable fungicides. Sodium hydroxide proved to be a poor fungicide in vitro.

When the various drugs just enumerated (and many others) are applied to skin it is at once apparent that there is marked variance in cutaneous tolerance to them. Thus, thymol must be used in high dilutions, and while its performance is excellent in vitro it is not quite so effective in clinical trial.

The prescriptions which we shall present may be found useful. It must be reiterated that the patient should be treated as an individual, the strength of the drug and the choice of vehicle depending greatly on the personal requirements.

It is customary to apply the medicament to the affected parts before retiring for the night. While this is usually the most convenient time, in many cases morning may be better. It is essential that the product be applied with pressure or massage, to insure the optimal effect. A smear or

a hasty application is almost useless. In many cases the preparation may be kept on the part day and night, being reapplied two or three times during the 24 hours.

1. A clean, efficient application for localized scaly noninflammatory intertrigo consists of 1 per cent tincture of iodine. The majority of persons may use this daily without its causing irritation.

2. Compound ointment of benzoic acid (Whitfield's ointment) is made as follows:

Benzoic acid	5 per cent
Salicylic acid	3 per cent
Soft paraffin	25 per cent
Coconut oil	ad. 100 per cent

In hot climates 2 to 4 per cent hard paraffin may be added. This is the ointment as originally advised by Whitfield. In this country the salve is often compounded in the following manner:

Salicylic acid	3 per cent
Benzoic acid	6 per cent
Hydrous wool fat, and	
Petrolatum	aa p.e.

This is referred to as "full strength." If there is considerable inflammation (but no vesicles) it may be used half-strength or even quarter-strength. If one desires a strong keratolytic effect it may be prescribed in double or triple strength. In general, this prescription, or a modification (to be mentioned), should be used only on the interdigital webs, the palms or the soles. On the dorsa of the feet, on the glabrous skin or on the backs of the hands it too frequently produces secondary inflammatory changes (which often become eczematous) to allow of its indiscriminate use on these parts.

Various other drugs may be added to modify the formula, the most commonly employed being iodine and chrysarobin. Both increase the irritability of the skin. It is advisable to begin with 1 per cent iodine or 0.25 per cent chrysarobin, later increasing the strength of either or both.

The vehicle also may be changed. White wax (2 to 10 per cent) may be added to diminish softening, particularly in hot weather. If alcohol is used, the strength of the active drugs should be decreased by one-third or more; a strength of 2 per cent salicylic acid and 3 per cent benzoic acid will be found potent. Aqueous solutions are not possible, owing to insolubility of the drugs.

3. A modification of Dreuw's ointment according to the following formula is sometimes very effective.

Rectified oil of birch tar	6 per cent
Chrysarobin	4 per cent
Salicylic acid	6 per cent
Soft soap, and	
Wool fat	aa 42 per cent

Because it is apt to produce secondary dermatitis, its use is somewhat restricted. When considerable inflammation is present, only a limited portion of the skin should be treated, so that if the condition is made worse, little harm is done.

4. The following prescription is usually well tolerated on the glabrous skin:

Sulfur	6 per cent
Salicylic acid	3 per cent
Hydrous wool fat, and	
Petrolatum	aa p.c.

The strength of both active ingredients may also be modified.

5. Mercurial products are mentioned because in vitro they show good restraining and fungicidal powers, although in clinical use they are rather disappointing. Phenyl mercuric nitrate provides an exception and at times is a useful fungicide. Levine found that it is best used in an ointment base in dilution of 1:1,500, when it is not a primary irritant.

6. Applied and allowed to dry on the affected skin, the following preparation has the advantage of being clean, and on the fortunate patient in whom pruritus is not induced it usually has a good clinical effect. It may be tried on vesicular lesions with caution.

Thymol	1 per cent
Salicylic acid	3 per cent
Alcohol (90 per cent)	q.s.

7. An aqueous solution of gentian violet (1 per cent) has been mentioned as valuable when there is marked inflammation. It may also be painted on chronic soggy intertrigos (some of which are due to M. albicans). There is little penetrating power, and it is not suitable for the treatment of areas of hyperkeratosis.

8. Another paint, first described by and named after Castellani, is somewhat irritating and must not be used on an acutely inflamed surface. It is effective as a fungicide and also possesses some keratolytic action.

Saturated solution of basic fuchsin	10
Aqueous solution of phenol (5 per cent)	100
Boric acid	1
Acetone	5
Resorcinol	10

Add the basic fuchsin to the solution of phenol and filter. Add the boric acid, after two hours the acetone and after two more hours the resorcinol. The solution should be kept in a dark bottle.

9. In many instances, particularly if the patient is working, it is impossible or inadvisable to have an ointment on the skin during the day. In this case a bath may be taken in the morning, followed by a liberal application of this powder.

Thymol	1 per cent
Boric acid	10 per cent
Zinc oxide	20 per cent
Purified talc	q.s.

Its beneficial effect may be attributed both to the active ingredients and to the value of any powder in combating perspiration.

10. A 10 per cent aqueous solution of silver nitrate is often effective if painted daily on localized macerated, fissured or exudative skin areas.

Many other drugs and prescriptions might be mentioned. Most of them, however, have little advantage except in providing a change, which is sometimes essential when the infection is long drawn out. The use of iontophoresis to introduce copper salts or other chemicals deep into the skin has been advocated. Greenwood and Rockwood found the method ineffective, a finding with which we concur.

The use of soap and water is usually permissible. In most instances, the patient should be encouraged to bathe. However, when an acute inflammatory condition exists, suspension of bathing, particularly with soap, may be best (see the section on prophylaxis for instructions on the care of the bathtub, p. 139).

During the past few years many investigators have evaluated the action of fatty acids, known to be protective against bacteria, as therapeutic antifungal agents. Laboratory tests indicate a favorable effect, although clinical trial is somewhat disappointing. Most of the acids in the concentration advocated (5 to 15 per cent) are relatively nonirritating in ointments or powders, an advantage in the treatment of a highly sensitized skin. At this time, undecylenic acid appears to be somewhat more potent than propionic acid and others of the fatty acid series. Hopkins and co-workers found undecylenic acid (5 per cent in carbowax, pH 6.8) to be the best local preparation in their extensive investigation. Muskatblit confirmed the lack of irritation from commercial preparations of undecylenic acid and salts. He thought this agent had some use in the therapy of tinea, although it was far from a superior fungicide.

(2) *Physical agents.*—There appears to be little if any advantage in the use of ultraviolet radiation. If the disease is of the inflammatory type, an induced reaction to ultraviolet rays may cause it to spread and to assume an eczematous character.

Roentgen rays, while not in themselves fungicidal, are frequently of great help in cases of severe inflammatory involvement. They are impotent in instances of infection due to T. purpureum, and little if any favorable effect will be obtained by directing them toward the interdigital webs. When there is an exudative inflammatory change the rays may be helpful either by aiding absorption of the exudate or by temporarily increasing the

acidity of the tissues. It should be reiterated that roentgen rays are dangerous unless employed with care and judgment and after study of the proper technic (see MacKee and Cipollaro, *X-Rays and Radium in the Treatment of Diseases of the Skin*).

(3) *Biologic methods.*—The use of biologic products (trichophytin) in the treatment of fungous eruptions (particularly dermatophytids) has been the subject of much investigation and subsequent discussion. Early reports (such as those of Van Dyck and others) were extremely optimistic. Sulzberger and Wise expressed their enthusiastic belief that a new and useful method of curing recalcitrant lesions had been brought forward. They reported cases in which cutaneous allergy to species of Trichophyton had been relieved by desensitization. Subsequent investigation has produced sharply divided opinions, ranging from that of Traub and Tolmach, who expressed doubt that trichophytin is of any therapeutic value, to that of Robinson and Grauer, who have obtained spectacular results with autogenous vaccines. Sulzberger later expressed his belief in the soundness of the conception of the principle of desensitization but admitted that the clinical response to treatment was poor. Combes and some others have held that the principle of desensitization is wrong, as a reduction in the immune forces may follow reduction in sensitivity. From our research, it seems that in most of the cases of actual fungous infection, an increase in sensitivity is desirable (provided this is linked up with acceleration of the immune forces). Thus, in the infections due to T. purpureum, the lack of reaction at the site of the trichophytin test after 48 hours is too frequent to be ignored as an explanation for the chronicity of this type of fungous disease. In dermatophytid, the condition should respond when the residual focus is eliminated. We believe that the diagnosis of dermatophytid is made much too often and that this reaction is relatively infrequent. The vesicular eruptions on the hands can be proved to be of mycotic origin in not more than one case in 10. In the cases in which theoretically trichophytin should be of service, it is unnecessary. In general, we do not at the present time advocate its use in treating either a definite fungous disease or an allergic manifestation (dermatophytid). This statement holds true for fungous infections due to any dermatophyte and in any site, including the scalp. Considering our results, we are unable to agree that the extravagant claims for one extensively advertised (South American) brand of trichophytin are justified.

A rational therapeutic attack in another direction has been attempted. Weidman and Chambers noted that some interdigital webs were free from fungous disease, and were often able to isolate Bacillus subtilis from this site. Subsequent implantation of the cultural growth of B. subtilis on

the sites of interdigital fungous infection was followed by clinical improvement. In studies along the same direction we were further influenced by the rapid overgrowth of many culture tubes by some of the common molds. Since 1944 we have had under observation in the laboratory a bacterial filtrate with a potent fungistatic capacity. This filtrate of Bacillus (subtilis) XG has shown promise of clinical value in the treatment of the superficial mycoses. From the reports of Tolmach and Lowenthal and of Hopkins and his co-workers, clavacin and some other antibiotics are also promising fungicides, although by no means superior to many of the standard remedies.

It is of interest that Belisario some years ago found lemon juice to be an effective fungicide. The work of Peck indicates that ascorbic acid has definite fungicidal and fungistatic properties.

(k) TREATMENT OF NAILS.—In the main, the indications for treatment and the principles underlying it are the same for the nails as for the skin. Because there are minor differences and additional therapeutic procedures, the treatment of the nails is considered separately.

If a fingernail is the site of an infection due to T. purpureum, it is probable that the feet and the toenails are also infected.

Infection due to T. gypseum may usually be cured by a combination treatment consisting of scraping the nail and applying fungicides. Roentgen therapy is sometimes useful. Evulsion of one or two fingernails may be carried out provided there is no other evidence of infection.

If the infection is due to T. purpureum, one is faced with a difficult therapeutic problem. The condition has probably been present for several months or even years, and infection of at least several nails is likely. There is probably also concomitant infection of the feet or of other regions. Complete evulsion of nails is not usually recommended here, as recurrence will almost invariably follow. Reliance must be placed on topical measures, after the nail has been scraped or as much nail substance as possible has been removed. If a sharp scalpel is available and the procedure is carried out with care, a surprising amount of nail can be removed without pain. Although there are important disadvantages to the office use of a burr powered by a small motor, its use has been gratifying in selected cases when patients purchased their own equipment and used it regularly to remove the infected nail material. One need not fear that the patient will destroy normal structures since pain will indicate when to stop. Newspapers should be spread over the floor to collect the material and a surgical mask should be worn. The topical application may be changed from time to time, and various medicaments may be used.

(*1*) *Complete surgical evulsion.*—Evulsion of a fingernail is not difficult,

but the proper technic should be carried out to the letter. We do not advise the evulsion of more than two or three fingernails. We almost never advise the evulsion of toenails because reinfection nearly always takes place and the procedure usually leaves the tissues so painful that the patient is kept from walking. Complete evulsion should not be considered when infection is due to M. albicans.

After sterilization of the overlying and surrounding skin with tincture of iodine, the paronychial tissue is infiltrated with procaine hydrochloride. The free border of the nail is grasped with a pair of forceps, and by blunt dissection the nail is progressively separated from its bed. Care should be taken not to break up the friable nail or, when the lunula is reached, not to destroy or injure the nail bed, since this would prevent or interfere with the return of a normal nail. The last attachment of the nail should be separated by tearing it gently across. Sterile gauze is applied with pressure until all bleeding is arrested. This usually takes from 10 to 15 minutes. The region is then painted with a 1 per cent aqueous solution of gentian violet, and a loose dry gauze dressing is applied. Since exudation may be expected, the dressing should be changed in two hours. After this a daily change of dressings is usually sufficient. Gentian violet should be applied each time the dressing is changed and daily for five or six days, after which the dressing is usually omitted. We do not advise the use of an ointment after the evulsion, particularly while exudation is still to be noted.

(2) *Roentgen therapy.*—When indicated, unfiltered roentgen radiation in fractional doses (90 roentgens) may be administered once weekly for six weeks. Further treatment is only given if cure is imminent.

(3) *Mechanical removal of infected nail tissue.*—A great deal of diseased nail tissue may be removed by the physician or technician by successive peeling with a Bard-Parker knife. (If care is used, a sharp blade will do no harm and does save time.) It has become our practice to use this method more often than formerly, repeating the procedure every two or three weeks. We have become more confident of ultimate success and are rarely disappointed, even in infections due to T. purpureum. As mentioned previously, the use of a revolving burr is of value for the same purpose. However it is difficult to sterilize and the infective material is widely disseminated. The patient should always be instructed to scrape the nail until the part becomes sensitive before any application. He may use a file or a piece of glass (the broken edge), and all removed nail should be collected on paper and burned.

(4) *Useful applications.*—1. Chrysarobin is probably the best single drug. It may be used in the strength of 20 per cent in collodion or 1 per cent in chloroform. There are other ways of using the drug, but these

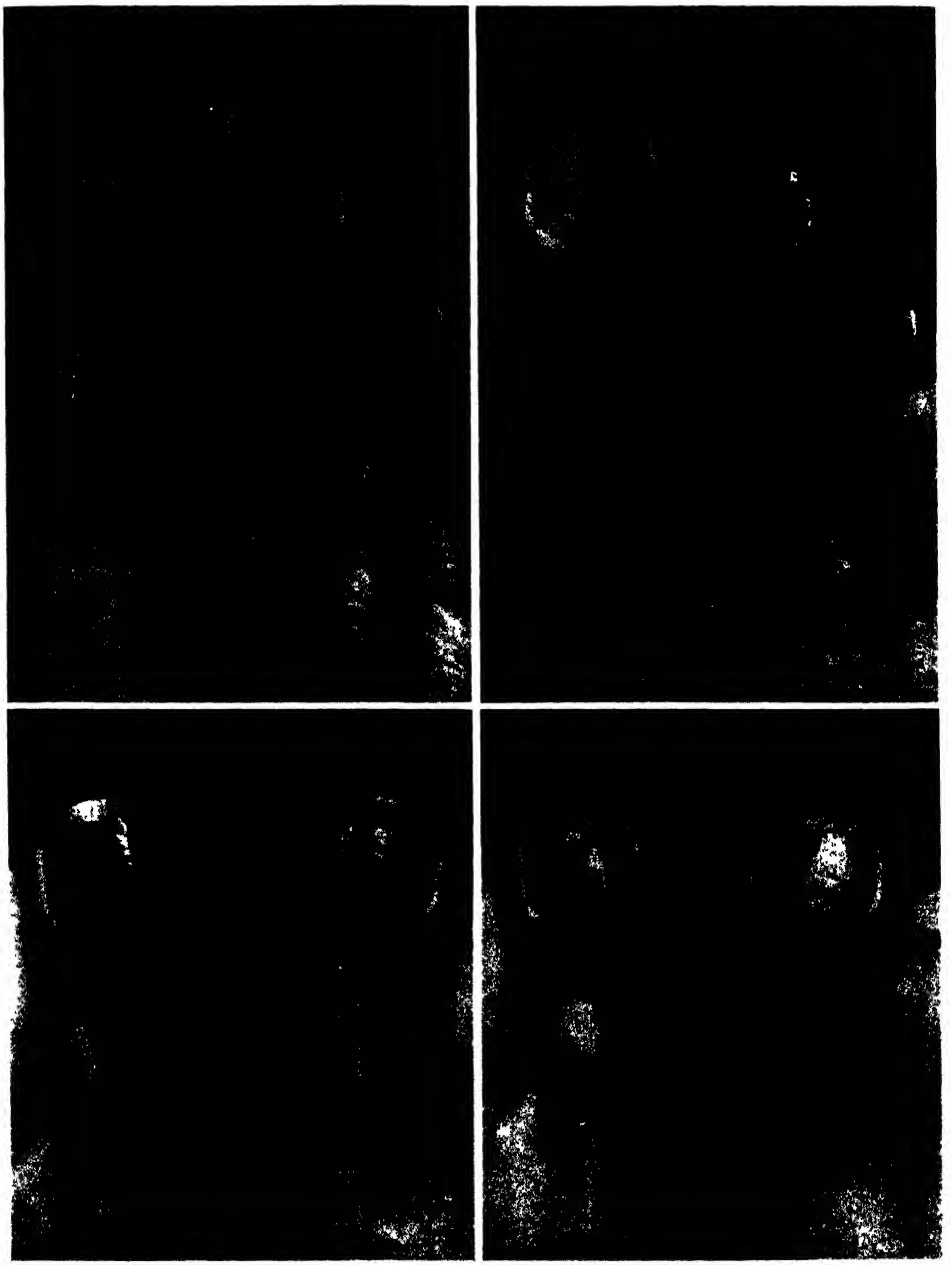

FIG. 45. Treatment of nails infected with fungi should include at least partial evulsion. With care, anesthesia is unnecessary. As much of the invaded nail as possible is cut away with a sharp scalpel. Medicinal agents then have more chance of direct action. The two top pictures show nails infected with M. albicans before and after partial evulsion. The two lower pictures are of nails infected with T. purpureum before and after the same procedure.

are the cleanest and probably the most efficacious. It should be remembered that chrysarobin is a cutaneous irritant and should be confined to the nail. Unless care is exercised that none comes in contact with the eyes, conjunctivitis may occur. As with all applications, the old medicament must be scraped away before any more is applied.

2. Salicylic acid is combined with benzoic acid in a salve (double-strength Whitfield's ointment), the proportions usually being 6 per cent of the former to 12 per cent of the latter. The obvious disadvantage of any ointment is that a great part of it is rubbed off; its use therefore is not only wasteful and unpleasant but somewhat ineffective. In order that these objections may be overcome, the surrounding skin should be covered with petrolatum and an adhesive finger cot should be applied to cover the entire end of the finger. Another useful application is a 40 per cent salicylic acid plaster cut out to fit the nail and changed daily. We can attest to its efficiency and cleanliness.

3. Resorcinol alone is not of much value, but it is useful in combination with other drugs.

4. Thymol is a strong fungicide. Its use on the skin may be attended with considerable reaction, but one need not worry over that effect in the treatment of nails. Thymol (2 to 5 per cent) may be combined with resorcinol (10 per cent) in an ointment and applied under adhesive covering, as mentioned previously.

5. Gentian violet and other dyes are not particularly efficacious in treating most cases of onychomycosis due to a species of Trichophyton.

6. We do not advise the use of copper sulfate as a soak to soften the nail. It has been recorded that in some instances gangrene has resulted from this treatment. In general we do not approve of the use of medicinal wet applications under an occlusive dressing for long periods, such as overnight. Softening of the nail may be partially secured by the careful application of potassium hydroxide (10 to 20 per cent). This may precede by half an hour or more the application of one of the remedies mentioned.

Finally, the patient should be made to realize at the outset that cure will require his faithful co-operation. Several months' therapy is usually necessary before all the fungi are destroyed.

(l) Prophylaxis.—The problem of prevention of infection with a pathogenic dermatophyte is difficult to solve. Many dermatologists believe that attempts to prevent infection are useless. It is their opinion that all the measures to be described and discussed here are of no avail and may even be harmful as tending to shift the emphasis to procedures which are time-consuming and of dubious benefit. The majority of uninfected persons are unwilling to be discommoded in any way when they have little conception

of the serious consequences which sometimes occur. At times one encounters persons who apparently have natural immunity, which may persist through life. Even those with interdigital maceration of the feet are frequently unconcerned or ignorant regarding the actual or potential presence of infection. Because of the ignorance or carelessness of the majority of uninfected persons or of those with latent involvement, certain measures to enhance protection to the public have been promulgated. It may again be mentioned that the chronic type of dermatophytosis (T. purpureum) may be overlooked.

The measures to be discussed are perhaps more generally necessary for patients who are in a state of remission (the largest percentage) and for those who have been cured of an attack of dermatophytosis. Apparent immunity sometimes follows a severe attack, but more frequently no immunity is conferred. We believe that cure of the chronic form of dermatophytosis is rarely accomplished and that relapse after an apparent cure is more common than reinfection.

Certain hygienic rules should be applied in the treatment of every patient with dermatophytosis. He should be made conscious of his responsibility to other members of his family and to those who use the same locker room, shower bath or gymnasium, whether at college, at a social club or at the less personal Turkish bath or sandy beach. The following discussion covers a few of the many points.

(*1*) *Patients apparently cured.*—These patients should receive the benefit of cultural studies. If results are negative, a prophylactic powder should be dusted on the skin after a daily bath, the skin having been carefully wiped dry. This treatment should be continued indefinitely.

Thymol	1 per cent
Salicylic acid	2 per cent
Boric acid	3 per cent
Purified talc	q.s.

(*2*) *Patients under treatment.*—1. The shoes, slippers and other footwear should be sponged out every few weeks with a 10 per cent solution of formalin. They should not be worn for 24 hours after an application in order that contact dermatitis may be avoided. Henderson and also Ayres, Anderson and Youngblood have found formaldehyde vapor an effective means of fumigation.

2. Cotton socks worn by patients with tinea pedis should be boiled for 10 minutes or immersed for half an hour in a 1:1,000 solution of bichloride of mercury. They may then be washed with soap and water or sent to the laundry. Woolen and silk stockings may be ruined by boiling, but the use of formaldehyde vapor in a box will be found effective.

3. The bathtub used by a patient with dermatophytosis should be washed

out with a 1:1,000 solution of bichloride of mercury or a 2:100 solution of cresol. A 5 per cent solution of formalin is also satisfactory.

4. The bath mat should be used only by the infected person. Once weekly it should be placed to soak in a 2 per cent solution of cresol and afterward washed. A newspaper spread over the bath mat should later be picked up and burned.

5. A patient may advantageously use paper slippers in walking to and from the bath. These may then be burned. Walking over rugs, carpets or bare floors may leave the infection for others to pick up. Pathogenic fungi may remain viable for several months.

6. It is unwise ever to scratch, pick or scrape an area of dermatophytosis with the fingernails. Most infections of the fingernails are thought to be derived directly from the feet.

(3) *Uninfected persons.*

A. Individual measures. Although, as previously mentioned, some people appear to have natural immunity, the fact that one does not have an infection is usually solely due to lack of contact with a pathogenic fungus. In order to remain free from dermatophytosis, one should observe the following precautions.

1. One should have a daily bath. The feet should be carefully dried, and purified talc, or better still a talc containing 1 per cent thymol, may be dusted liberally under and between the toes. If other members of the household are infected and use the tub, chlorine may be added to the bath water.

2. Loose and dead skin should be removed, and nails should be kept trimmed. Callosities should be treated. Fungi grow in horny material.

3. Attention should be given to flatfoot or other orthopedic conditions. These predispose to hyperhidrosis, which in turn favors invasion of a pathogenic fungus.

4. Hyperhidrosis may be relieved by roentgen therapy or by soaking the feet for two to 10 minutes daily in a 25 per cent solution of formalin. Only sufficient solution is placed in a basin to cover the sole and reach part way up the sides of the foot. The solution is too strong for the dorsum of the foot.

5. As a rule one should avoid public bathing places and Turkish baths. If possible, one should refrain from walking on carpets, rugs or bare floors. If in a hotel, one should walk to the bathroom in slippers and place newspaper on the bathroom floor to stand on. The tub or shower should be washed out with hot water if no antiseptic is available for this purpose.

6. If one visits a public beach or bathing resort or other place where exposure is likely, the feet should be painted as soon afterward as possible

with a 1 per cent aqueous solution of gentian violet or 1 per cent tincture of iodine, particular attention being given to the inner and under surfaces of the toes.

7. One should avoid persons known to have the disease. If a member of the family is infected, one should see that he is under treatment, that he uses his own bath mat and towel, that he does not walk around in his bare feet and that the tub is washed out with an antiseptic after he uses it.

B. Public health measures. Since one cannot depend entirely on individual responsibility and initiative, a number of attempts have been made to protect the uninfected by measures carried out by those in authority in various institutions.

A commonly used method is to place a solution in a convenient place so that persons using a swimming pool will have to walk through it in passing to and from the pool. According to Claassen, sodium thiosulfate (10 per cent), which has been advocated, will support the growth of fungi in culture. Osborne has drawn attention to the fact that sodium thiosulfate if used near swimming pools is carried into the water and neutralizes the sodium hypochlorite, thus exposing the persons in the pool to bacterial contamination. Sodium hypochlorite (1 per cent), first advocated by Osborne and Hitchcock, seems to have more adherents. The solution must be changed frequently (every 48 hours). Sodium hypochlorite may be purchased from many chemical houses in a 20 per cent solution and diluted with water in the ratio of 20:1 for use in the pans. Tile floors should be washed with a cresol solution once daily.

Prophylaxis may be easily attained with a mild fungicidal powder, such as has been mentioned. It should be placed conveniently for use after the bath.

Such a simple procedure as the daily application of a powder was advocated for general use to prevent dermatophytosis among the armed forces. Under conditions of active combat, a powder is more easily carried than ointment or liquid. A preparation containing 1 per cent thymol (fungicide), 2 per cent salicylic acid (keratolytic) and 3 per cent boric acid (to alter the pH) in talc is theoretically sound and has been found effective in practice.

In many modern schools and colleges, students found harboring an active or latent fungous infection are excluded from the recreational facilities of the institution until the disease has been cured.

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6. MONILIASIS

This disease syndrome embraces a number of manifestations which until recently were considered to be unrelated. Although the skin is the most common site, the infection may invade the lungs and, rarely, other organs. The causative fungus is a yeastlike organism, Monilia (candida) albicans.

(a) HISTORICAL SURVEY.—In 1839 Langenbeck demonstrated fungi in material taken from a patient with thrush. Robin published a description of the micro-organism in 1843 and named it Oidium albicans. The various manifestations of the disease were recognized and studied by different investigators, and an involved nomenclature came into use. Through the work of Kaufman-Wolf, Fabry, Kumer, Ravaut, Hopkins, Benham and others, the relationships of the various rashes and conditions have been better understood. Schamberg, in 1915, was one of the first in the

United States to report a case of generalized cutaneous thrush. Engman in 1920 described a case of moniliasis localized to the upper parts of the thighs, the vulva and the inframammary regions. The article by Shelmire and that by Beeson and Church were also early contributions.

(b) ETIOLOGY.—The causative micro-organism, M. albicans, is seldom if ever found on the normal skin. Other yeastlike fungi should not be confused. The organism is a common inhabitant of the gastrointestinal tract, where it may produce no symptoms. While it was formerly considered, mainly through the investigations of Ashford, to be of etiologic significance in sprue, later research does not appear to bear out such a relationship.

The incidence of infection increases with age. There is a more or less corresponding increase with age in the involvement of the gastrointestinal tract. Relapse of cutaneous lesions may take place when a systemic or debilitating illness is experienced. The resistance of the patient to M. albicans is decreased by diabetes, probably because the storing of sugar favors the growth of the organism. We have noted that a large percentage of the patients with different types of cutaneous moniliasis are obese. The organism is more apt to find suitable soil in persons whose skin is macerated by frequent or prolonged immersion in water. Profuse sweating may be followed by moniliasis. Housewives, bartenders, waiters and bakers appear to be more prone to the condition because of their occupations. The organism is probably of weak pathogenicity, but once the disease state is established, through a letdown in the natural immune forces, the condition is apt to persist indefinitely. The organism multiplies rapidly; it may be isolated from such diseased tissues as those of carcinoma, and it may be found in the sputum of a patient approaching death. In such instances, one must be careful to differentiate between the saprophytic and the pathogenic significance. It is probable that the virulence of M. albicans may so increase that the fungus is capable of causing an infection without any apparent predisposing factor. The series of cases of perlèche of children in an orphanage, as reported by Finnerud, may be cited as a possible example.

(c) THE CLINICAL SYNDROME.—The manifestations of M. albicans may be grouped as (1) localized, (2) of moniliid type, (3) generalized cutaneous and (4) systemic.

(*1*) *Localized forms.*

A. Onychia and paronychia. It is chiefly the fingers which are affected, although we have observed instances of infection of the toenails. There may be involvement of only one digit, but multiple infections are more frequently seen. The paronychial tissues are usually the first to be involved,

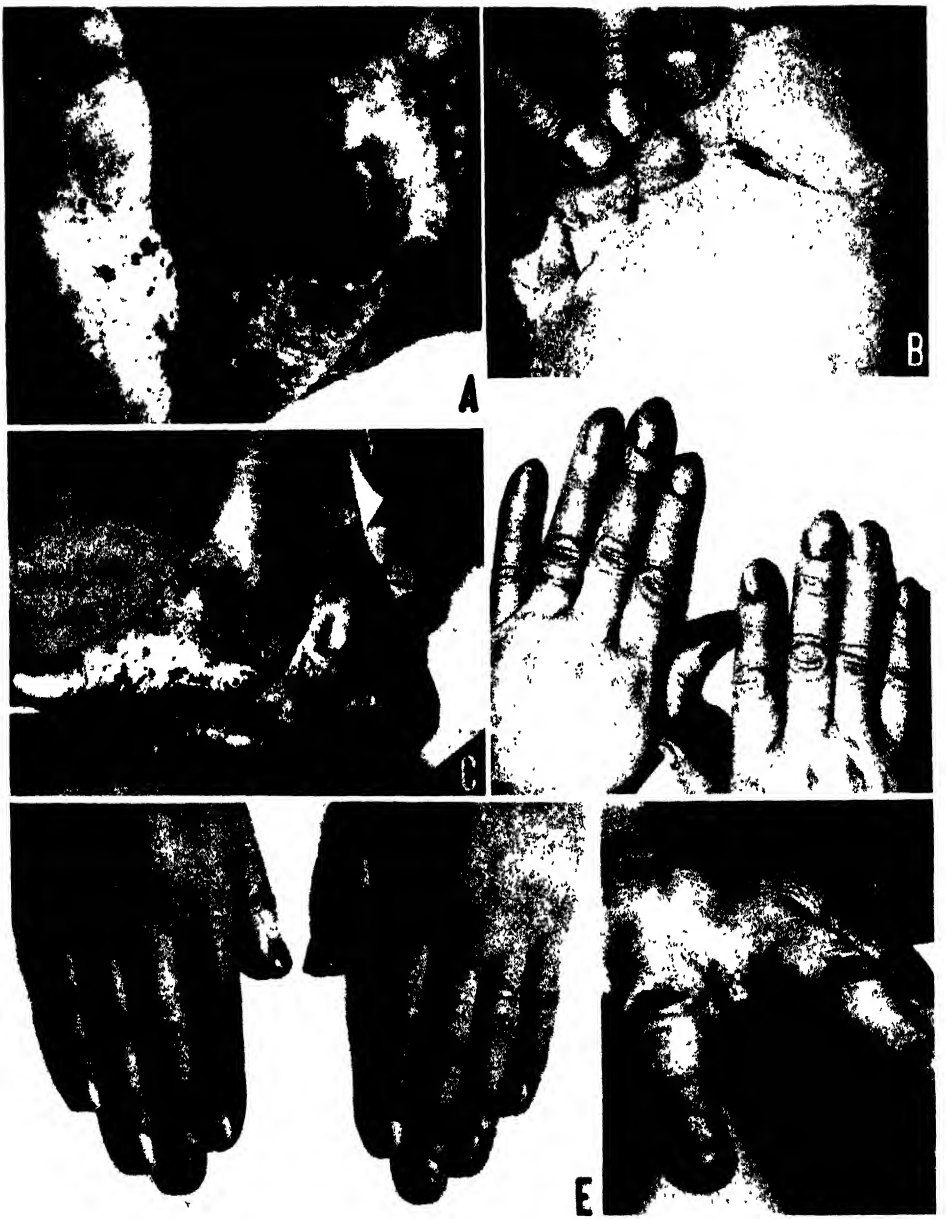

FIG. 46. Moniliasis of the feet and hands. *A*, acute exudative soggy vesiculobullous infection. *B*, chronic thickened scaly rash with moist intertriginous involvement of all the webs. *C*, eruption spreading to sides and dorsa of feet. *D* and *E*, onychia and paronychia. The changes of the nail may be due to nutritional conditions. Invasion of the nail at the sides is rather typical of M. albicans. *F*, erosio interdigitalis blastomycetica or intertrigo of a finger web. (*A and C, courtesy of Royal Montgomery.*)

and the condition may appear not unlike a pyogenic infection. There is usually little or no pain except on pressure, but sometimes the parts throb. No pus will be found if the tissues are incised; a thin purulent discharge may appear under the nail fold. In the nail, transverse ridges are noticed. The nail remains hard but gradually becomes thickened and distorted, particularly at the edges. The color may not change or it may become brownish. Usually the shine is unaffected. The proximal portions or the edges of the nail sometimes become eroded. It is at once apparent that the cardinal signs of tinea unguium, namely, crumbling, yellow color and loss of luster together with lack of paronychia, readily distinguish the two conditions.

B. Intertrigo. Well defined, bright red, exuding patches with scalloped borders give a fairly characteristic picture of monilial intertrigo. Outside the zone of intertrigo, small flaccid vesicopustules may be noted. There is usually a bright red border of skin around the satellite lesions. According to Hopkins, these represent the primary lesions from which intertrigos develop. The common sites of monilial intertrigo are the axillae, the inframammary folds, the groins, the umbilicus, the interdigital webs of the feet and the intergluteal fold. The process may extend from a primarily intertriginous location to the flat skin, and large sheets of skin of a susceptible person may be affected. It may be pointed out that interdigital involvement of the toes may be mistaken for dermatophytosis caused by filamentous fungi. In case M. albicans is the cause, all the webs of the toes are usually involved. A bright red color and soreness with satellite vesicopustules also favor a diagnosis of moniliasis. Lesions of a similar nature on the hands and at the angles of the mouth have distinct names.

C. Erosio interdigitalis blastomycetica. This form of intertrigo affects the interdigital webs of the hands (usually the third or fourth). The lesion has a bright red base with a moist surface and a peeling border. The lesions are tender rather than itching.

D. Perlèche. This type of intertrigo affects the angles of the mouth. The base is bright red, the surface may show a pellicle of skin, and fissures commonly develop. Some cases of perlèche are said to be due to infection with streptococci. Avitaminosis may be a predisposing factor.

E. Asymptomatic gastrointestinal form. The presence of M. albicans in the saliva or in the stools of patients with no symptoms referable to this and with no concomitant involvement of the skin suggests that many persons are carriers. With many forms of moniliasis of the skin, organisms can also be located in the gastrointestinal excreta. In the treatment of perlèche, cure is often difficult unless the mouth is treated at the same time.

F. Intraoral thrush. Thrush is most commonly seen in infants and some-

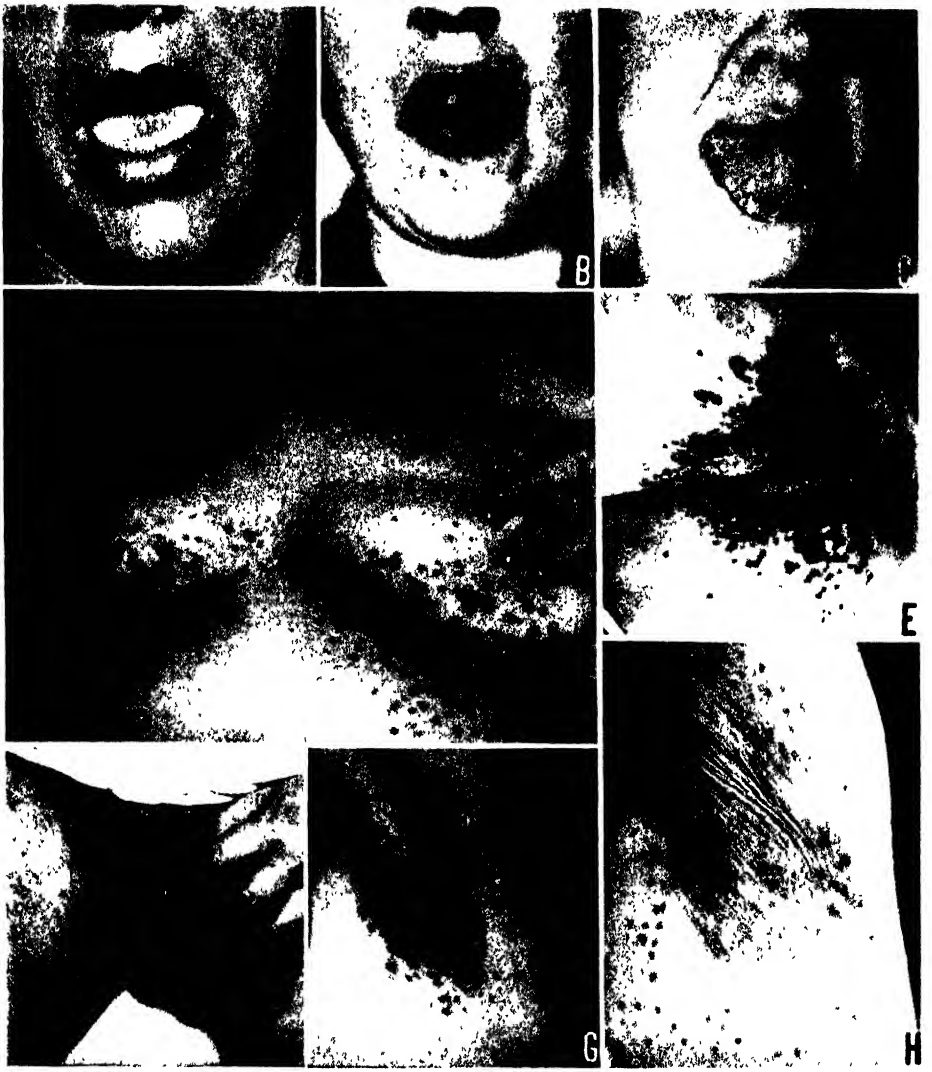

FIG. 47. Moniliasis, showing types of involvement of the skin. *A* and *B*, perlèche. *C*, beefy-red, smooth tongue. *D* and *E*, inframammary intertrigo; note the outlying satellite lesions. *F*, intertrigo in the inguinal region. *G* and *H*, intertrigo of the axilla.

times in babies only a few days old. A whitish, loosely adherent membrane is attached to the inner surface of the cheeks or to the palate and sometimes to other portions of the oral mucosa.

G. Superficial glossitis. This is manifested by a beefy-red, smooth, sometimes mottled or enlarged, tongue. Stomatitis is often associated.

H. Water bed dermatitis. Kumer and others noted that many patients acquired an eruption when kept in continuous baths, when wet applications of bland nature were applied over long periods or occasionally when occlusive dressings were left on a part for a considerable time. The affected skin is macerated and peels off, a red base may be noted, and satellite vesicopustules may be present. It is to be noted that other yeastlike micro-organisms may be present, and, as with M. albicans, they may be living a solely saprophytic existence.

I. Eczema. White and others have noted the occurrence of yeastlike organisms in cases of typical infantile eczema. There is some doubt as to whether M. albicans is able to cause this type of response. Many instances of secondary cutaneous thrush (in children) or of moniliids may be mistakenly considered to be eczema.

J. Vaginitis. The finding of M. albicans in the vagina does not necessarily denote more than an asymptomatic involvement. There is little doubt, however, that the organism may produce vaginitis with a low grade inflammatory response accompanied by a thin discharge. Pregnancy and diabetes are considered to be important conditioning states. Pruritus may be a troublesome symptom. Rubbing and scratching often lead to secondary pyogenic infection and eczematization, either or both of which may become sufficiently severe to mask the original infection. It is believed that thrush in newborn infants may be secondary to infection of the vagina.

K. Pruritus ani. In cases of severe itching, when one notes considerable maceration around the anal orifice, M. albicans may be the cause.

More than one of the localized types of infection may be present in the same patient.

(2) *Moniliids, or levurides.*—Sterile vesicular lesions on the hands and localized or widespread erythematous vesicular exudative patches caused by dissemination through the blood stream of products of M. albicans have been described by Ravaut and others. According to Hopkins, certain cases of miliaria are due to M. albicans. The condition is probably a moniliid, although Hopkins found the organism in some of the lesions. A focus may be found elsewhere on the skin, but according to Hopkins the gastrointestinal tract is a frequent site. The diagnosis of moniliid of the hands is similar to that of trichophytid. Sometimes the absence of a fungous focus on the feet will make one suspicious of moniliid (rather than trichophytid).

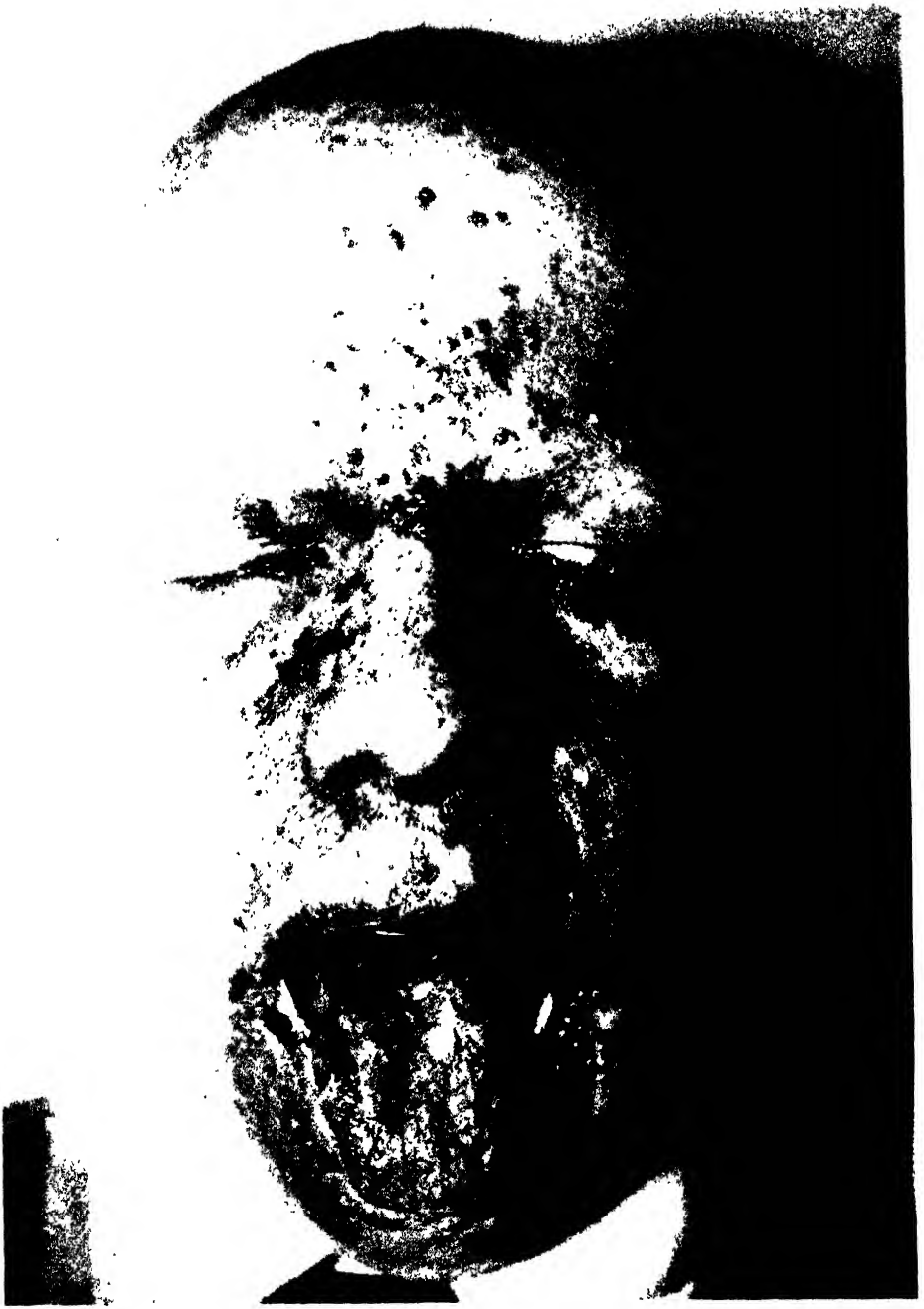

FIG. 48. Moniliasis of generalized type, showing discrete flat pustules, exudative inflammatory patches (suggestive of seborrheic eczema), perlèche, beefy tongue with membranous plaques and diffuse loss of hair on the scalp and eyebrows. The fingers, toes and other parts of the body were also affected. (*Courtesy of Wilbert Sachs.*)

(*3*) *Generalized cutaneous forms.*—A fortunately uncommon manifestation seen in children is the type in which the hair of the scalp is sparse and the scalp partially inflamed, with perlèche and glossitis present as well as other types of localized infection. The patient also may exhibit widespread eruptions of the glabrous skin. Characteristic flat pustules may be observed in some part of the eruption. The infection may last for many years and be extremely resistant to therapy, and in some instances the outcome may be fatal.

(*4*) *Systemic forms.*—Greenwood and Rockwood and others have reported instances of fatal systemic infection. This may be superimposed on the type just discussed. Involvement of the meninges has been described. In some instances bronchitis has also been considered to have a monilial source. The finding of Monilia in the sputum in cases of suspected bronchial moniliasis is not sufficient to establish a definite diagnosis, since the organism is often present in the mouth and in the gastrointestinal tract. In a patient with symptoms referable to the lungs, when repeated tests for the tubercle bacillus have been fruitless, a mycotic disorder may be suspected. The roentgenogram showing a mycotic disease of the lungs may reveal shadows and densities of varying degree, often confined to the base. Since the exact diagnosis is not a purely theoretic problem, in case of doubt specimens should be obtained after bronchoscopic study. It should also be remembered that yeastlike fungi are notorious secondary invaders; their presence in diseased tissue does not always mean that they are responsible for the disease. The presence of M. albicans in diseased tissue is not always sufficient evidence of its pathogenicity, and in some cases the cause of the condition is difficult to ascertain. It is often necessary to study a patient for some time before a definite diagnosis can be made. Castellani described monilial bronchitis affecting tea-tasters of Ceylon. This is a relatively banal infection with periodic flare-ups of a productive cough lasting for years but finally disappearing spontaneously. More severe infections of bronchopneumonic type are uncommon. A presumptive diagnosis is in order after repeated examinations (including gastric washings) have been negative for tubercle bacilli if massive amounts of the fungus are observed in the sputum on several occasions. Joachim and Polayes reported the case of a white man, 48, who had been addicted to the use of morphine and heroin for 20 years. For 18 months he injected the drug intravenously. Systemic manifestations developed and he finally died of subacute endocarditis. A species of Monilia was obtained in blood cultures and from vegetations on the heart valves. Wikler and his associates also reported the case of a drug addict who died of mycotic endocarditis, the organism being M. parapsilosis.

(d) HISTOLOGY.—It is advisable to scrape the biopsy material for culture. Mycelium is sometimes demonstrable in section but a diagnosis on this alone is impossible. The findings are usually those of a chronic inflammation with round cells and occasional giant cells.

(e) DIFFERENTIAL DIAGNOSIS.—Usually, little difficulty is encountered in recognizing the localized forms of moniliasis and distinguishing them from similar disorders. Intertrigo of the feet may occasionally be puzzling, and areas of widespread involvement, especially if they have been overtreated, may be difficult to recognize at first. Pyodermic infection and tinea due to Trichophyton are easily distinguished by the acute painful paronychia associated with the former and by the lack of paronychia and the presence of a yellow friable nail with the latter. The moniliids are not as definite an entity as one would desire, and the diagnosis must frequently be ascertained by the exclusion of other diseases. Severe generalized involvement should not be confused with any other disorder, although in some instances it is mistaken for seborrheic eczema, and there may be slight resemblance to disseminated neurodermatitis (atopic eczema). The greasy scales of the former and the lichenification present in some areas of the latter, together with the lack of flaccid vesicopustules and negative results of cultural studies should be sufficient to distinguish these diseases. The oidiomycin test is of no value in differential diagnosis. Demonstration of the organisms in culture from lesions of moniliasis is usually readily accomplished. As mentioned previously, tuberculosis must be distinguished from monilial bronchomycosis.

(f) PROGNOSIS.—Patients with any form of moniliasis should be considered potentially diabetic. The infection may be the first manifestation of diabetes. The local varieties usually respond to treatment, but relapse may occur. It is difficult to eradicate the micro-organism from the gastrointestinal tract. Generalized involvement and moniliids are resistant to therapy, and cure may require months or years. When infection is generalized, the prognosis should be reserved; in cases of systemic involvement the outcome is often fatal.

(g) TREATMENT.

(*1*) *General instructions.*—If it is to be comprehensive and permanently effective, therapy should be directed toward the eradication of all foci, both in the skin and in the gastrointestinal tract. Unfortunately, treatment of the latter is not highly effective. Infection caused by M. albicans calls for urinalysis, to determine whether an otherwise asymptomatic glycosuria is present.

The treatment of infections of the skin caused by M. albicans depends partly on the site of the disorder and partly on the individual patient.

When the hands are affected, it is important to keep them from frequent immersion in water. The use of cotton and rubber gloves may protect them to some degree. Improvement in hygiene may be helpful in preventing the development of lesions. Multivitamin supplement to the diet is indicated. We have not had much success with low caloric diets. Most of our patients did not wish to reduce their weight.

Hopkins noted that a patient with generalized cutaneous moniliasis and with involvement of the gastrointestinal tract improved while on a diet free from bread, cereals, potatoes and other starchy vegetables and with the use of dextrose instead of cane sugar. Magnesium carbonate and calcium carbonate were given in large doses.

(2) *Local treatment with gentian violet.*—Churchman first introduced this substance as effective in the treatment of infections caused by gram-positive organisms. Gomez-Vega noted that the growth of organisms of the genera Monilia and Torula, when tested in vitro, was inhibited in dilutions of 1:1,000,000 of gentian and methyl violet. Cornbleet found gentian violet more effective when followed by an application of Gram's solution of iodine. We subscribe to the opinion of many observers that a 1 per cent aqueous solution of gentian violet is probably the best single topical remedy against Monilia infections of the skin. It may also be used in the treatment of oral thrush. We have used it with success in suppositories (2 gr. [0.13 Gm.] to each) in the treatment of monilial vaginitis and pruritus ani due to M. albicans. The chemical may also be incorporated in zinc paste. Sutton has written a comprehensive article on the uses of gentian violet in dermatology.

(3) *Local treatment with other applications.*—Many other advocated local remedies are useful in certain instances. Wet dressings are almost always well tolerated and are often an acceptable means of beginning treatment. A solution of 1:2,000 potassium permanganate or a 1:5,000 solution of perchloride of mercury applied for a few days in continuous wet dressings to areas of local infection often brings about considerable clinical improvement. Sodium perborate as a mouthwash and a 1 per cent solution of silver nitrate in nitrous ether have proved of value in many instances of monilial intertrigo. Ormsby recommended chrysarobin in strengths of 5 to 10 per cent, tincture of iodine or an ointment containing salicylic and benzoic acids. Mercurial preparations, such as ammoniated mercury ointment (3 to 10 per cent), are more effective against moniliasis than against ringworm infections. Soothing applications, such as zinc oxide lotion or wet compresses of boric acid, are sometimes necessary when acute inflammation is present.

(4) *Roentgen therapy.*—Roentgen rays are useful in the treatment of

paronychia and onychia and are also sometimes effective in the treatment of perlèche. The usual dose is 90 roentgens administered without filtration once weekly for four to six treatments.

(5) *Treatment with iodides.*—We have had limited experience in the administration of potassium iodide by mouth in the treatment of the localized forms of moniliasis. In some instances we have given the medication to the point of evidence of intolerance. Our results, however, have not been conclusive, and we have not observed any cures. Lugol's solution diluted one-half with water is a nonirritating application which we have used successfully in the treatment of oral thrush as well as in other types of moniliasis. In an apparently hopeless case of the systemic type of moniliasis observed by MacKee, M. albicans was isolated from the skin, gastrointestinal tract and sputum. Treatment by topical applications of gentian violet together with daily inhalations of ethyl iodide according to the method of Swartz resulted in marked clinical improvement. When last observed, the patient was in excellent condition.

(6) *Vaccine therapy.*—There are not many reports in the literature regarding the efficacy of this form of therapy. Sulzberger and Wise and later Kerr, Pascher and Sulzberger reported successful quantitative intracutaneous therapeutic desensitizations with Trichophyton and Monilia extracts, alone and in combination. Olah tried autovaccine therapy without success in cases of onychia and paronychia.

In a series of 48 patients, we used intracutaneous injections of oidiomycin. The patients received from six to 44 injections, the average number being 11. The vaccine was administered in dilutions of 1:1,000 to 1:500, 1:100 and 1:50, beginning with the more dilute and proceeding to the more concentrated doses. The patients were given a bland application for topical use, for the most part a colored petrolatum. No absolute cures were noted, but there was an apparent improvement in the condition of a few of the patients. In the great majority of cases no improvement was noted. In no case was there any harmful complication, such as an exacerbation of the eruption or a focal reaction.

(7) *Other measures.*—When the infection is severe, attention to the general health and measures to build up bodily resistance, such as vitamin therapy, a nutritious diet and added rest, may be of primary importance.

In the treatment of Monilia infection of the nail the patient should be told to avoid soaking the hands in water, particularly with soap, to avoid the peeling of unwashed vegetables and to dry the skin carefully after washing the hands. If possible, a housewife should arrange to do all the scrubbing or washing at one time of the day. Roentgen therapy may be used. A 1 per cent aqueous solution of gentian violet may be applied at

the base of the nail and gently inserted under the nail fold with an orange-wood stick. Chrysarobin in collodion (5 to 10 per cent) may be painted over the paronychial tissues once daily. Boric acid ointment and sodium perborate paste are other useful topical remedies.

In the bronchopulmonary and pulmonary forms, potassium iodide should be administered in ascending doses over prolonged periods. In some cases there seems to be an advantage in employing ethyl iodide by inhalation. Gentian violet, intravenously, has been advocated by Stovall and Greeley.

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7. TINEA VERSICOLOR

This disorder, also known as pityriasis versicolor and chromophytosis, is a common superficial mycosis readily recognized and treated. The condition is chiefly of importance cosmetically. However, there are several interesting facts about the disease and its management.

(a) ETIOLOGY.—The micro-organism causing tinea versicolor is known as Malassezia furfur. The disease affects young adults (of both sexes) by preference, but we have observed instances of infection in children and in the aged. While social standing is not important, the lack of personal hygiene, more common in the dispensary patient, predisposes to infection. Some persons appear to be rather susceptible. Hyperhidrosis is said to predispose. Several members of a family may be infected. Contrary to an old tradition, the disease is apparently not more common in patients with pulmonary tuberculosis. The usual physical examination of such persons probably led to the discovery of the disease, and its equally frequent inhabitation of the skins of other persons was not realized. While the disease is probably not more common in the summer than in the winter, patients with the disorder are usually seen in the warm weather, when its presence is more evident.

(b) CLINICAL DATA.

(*1*) *The usual symptoms.*—The disease manifests itself by scaly macules and patches starting from barely visible lesions in single or multiple foci. The color varies from that of the skin to dark brown. It is said that the usual color is yellowish fawn, but the shade varies with the season. During the winter the color may be that of the skin or light brown. In the summer, particularly toward the end, the color becomes darker and may be of a chocolate shade. Usually no inflammation is evident. The surface of the affected skin is sometimes noticeably scaly, but often a scratch is necessary to dislodge the scales. Cases of follicular involvement are rarely observed. In such cases the lesions remain small and may become slightly elevated.

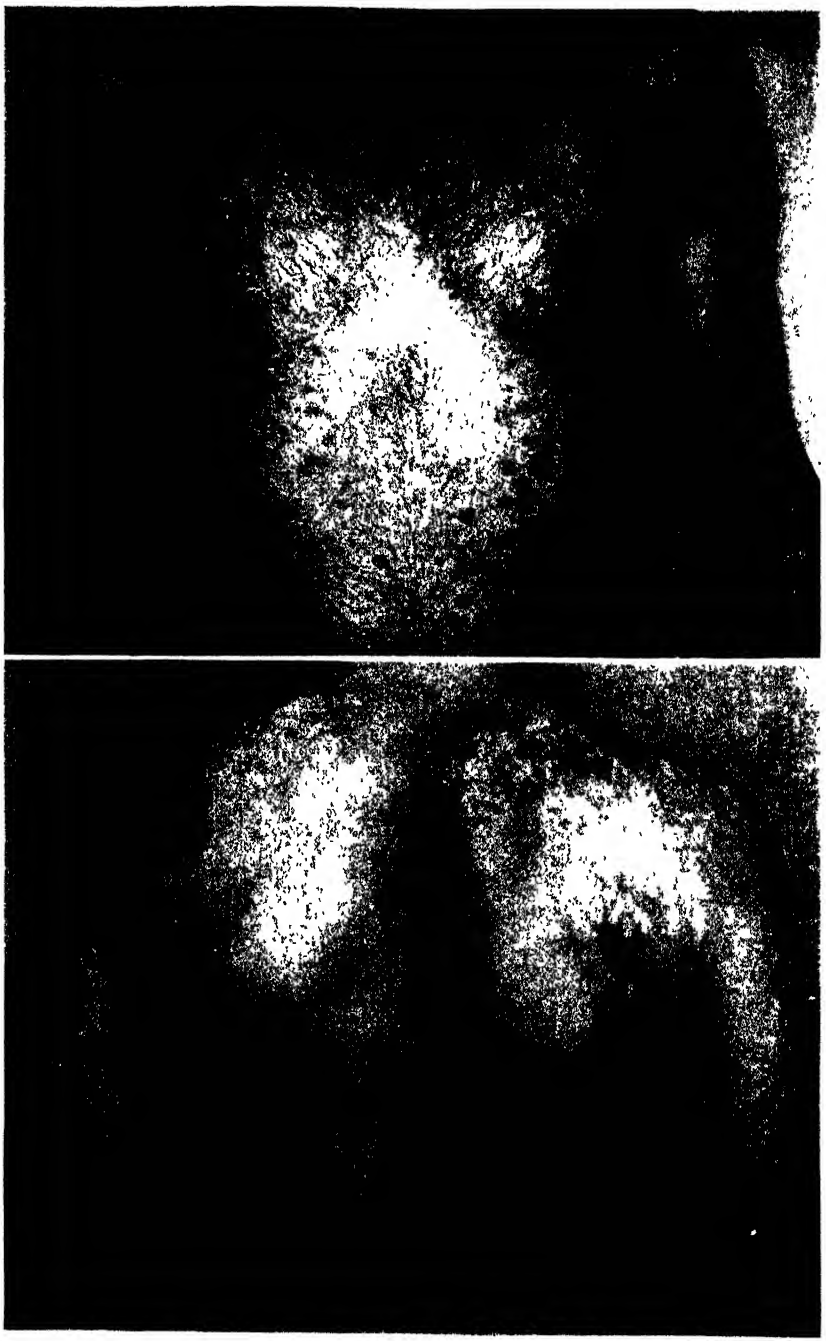

FIG. 49. Tinea versicolor, or chromophytosis. *A*, typical brownish scaly patches, usually most marked on the torso. The color varies with the season, being darker in the summer and lighter during the winter. *B*, pseudo-achromia caused by the screening effect of the lesions during exposure to ultraviolet rays. This may be mistaken for vitiligo.

FIG. 50. Tinea versicolor of the papular follicular variety, very rarely observed. (*Courtesy of George M. MacKee.*)

The sites of predilection are the chest, the abdomen and the back, but the condition may attack any part of the skin, including the scalp and the palms and soles. Baer noted an instance of involvement of the face and scalp. We have observed a number of instances of infection on the back of the neck, and the extensor surface of the arm above the elbow appears to be a common site. At times the eruption favors intertriginous locations, such as the axillae, the inframammary folds or the inguinal regions; adiposity may predispose to the involvement of these regions. The disease sometimes involves large sheets of skin, and the manifestations may be extreme. Mild itching may be present. There is little if any tendency to spontaneous cure.

When lesions of tinea versicolor are examined under filtered ultraviolet rays, fluorescence is noted; this varies from golden yellow to dark brown (depending on the amount of pigment in the lesions). This fluorescent characteristic has proved of interest and value not only in establishing a diagnosis but in determining the extent of the eruption. Changes of the color of the skin may be invisible in ordinary light but will be readily detected when a thorough cutaneous inspection under filtered ultraviolet radiation is undertaken.

(2) *Pseudo-achromia.*—During the summer or autumn, a patient with tinea versicolor not uncommonly exhibits light-colored (apparently depigmented) areas on the surfaces of skin exposed to sunlight. These areas usually appear suddenly after sunburn followed by peeling, although a history of a visible reaction is not always obtained. The patches occupy the sites of lesions of tinea versicolor; they are irregular and of various sizes and appear chiefly on the trunk. Their color is not the dead white of vitiligo, although because of their contrast to the surrounding skin, especially in persons of dark complexion, they may be mistaken for that disease. Areas of skin on the covered parts of the body are usually found to match in color the achromic-appearing spots. There is no increase of pigment at the periphery of a lesion. A scarcely perceptible scaling may be noted. Sometimes the condition appears year after year, becoming less noticeable during the winter and reappearing during the summer.

The light areas do not, as a rule, become tanned after further exposure to ultraviolet radiation; on the contrary, they become more and more noticeable, owing to the increase of pigment in the surrounding normal skin.

Examination for fungi combined with observation of the patient under filtered ultraviolet rays reveals that organisms are frequently present in these light patches. Some writers have expressed the opinion that there is definite achromia. Our inquiry into the nature of the lightening of the skin favored the theory of mechanical screening of the sun's rays, suggesting that the skin was light by contrast to the surrounding, normally pig-

FIG. 51. Hidden lesions of tinea versicolor. *A* indicates that clinical inspection does not show the infection. During the winter the color of the patches may be similar to that of the skin. *B*, lesions outlined as they were revealed under filtered ultraviolet rays.

mented skin. A mechanical cause was indicated by the facts that (1) the dopa reaction revealed a normal amount of pigment in the skin; (2) the scales of tinea versicolor protected the skin from ultraviolet rays to a greater degree than the scales of psoriasis or of pityriasis rosea; (3) fluorescent material from cultures of other fungi possessed a screening effect against ultraviolet radiation, and (4) increase in pigment in a patch was possible only when the overlying micro-organism had previously been treated and destroyed.

(c) IMMUNE REACTION.—There is no acquired sensitivity to trichophytin. Since the cultivation of M. furfur is still a matter of conjecture, specific sensitization to a vaccine remains to be proved. Since the process is superficial and no involvement of the cutis is to be observed, sensitization is unlikely.

(d) DIFFERENTIAL DIAGNOSIS.—The ordinary form of tinea versicolor can hardly be confused with any other disease. If of limited extent, it may simulate chloasma. Since the organism can be readily demonstrated and since the appearance under the filtered ultraviolet rays is characteristic, there should be no mistake.

With pseudo-achromia of tinea versicolor, however, certain other diseases may be considered.

(*1*) *Achromie parasitaire à recrudescence estivale.*—From the published description of Jeanselme it appears that this disease is pseudo-achromia of tinea versicolor.

(*2*) *Achromia parasitaria.*—It is difficult to fit together the varied symptoms in the syndrome which Pardo-Castello and Dominguez described. In some cases irregular, dirty-white macules and patches which are slightly inflamed, scaly and somewhat itchy are present on the face and neck. In other cases the eruption is generalized, no inflammatory symptoms are present, and the disorder simulates the pseudo-achromia of tinea versicolor. In one of the illustrations in the article by Pardo-Castello and Dominguez are shown lesions on the trunk which suggest the last-mentioned disease. In both disorders, the scaling in the early macules is white and furfuraceous and the older lesions are devoid of scales. There is no increase of pigment at the edges. The mucous membranes, hair and nails are not affected. In the series reported by Pardo-Castello and Dominguez there were four cases in which the disorder was generalized, the palms and soles being free. Aspergillus was cultured in six of 36 cases and was considered a possible cause of the disease. No mention was made of examination of scales in potassium hydroxide for the presence of M. furfur. In a later communication, Pardo-Castello expressed his belief that the same clinical picture may be found in patients of different races and in persons residing in differ-

ent countries, that it may affect different types of persons and that it may be caused by a variety of organisms. He did not believe that the rays of the sun play any part in the cause. Further investigative work appears necessary to clarify the picture.

(3) *Tinea flava or tinea versicolor tropicalis.*—Castellani stated that this condition is identical with achromia parasitaria (Pardo-Castello and Dominguez). The fungus responsible cannot be distinguished from M. furfur in potassium hydroxide preparations, and like that organism it is nonculturable. Castellani differentiated tinea flava from tinea versicolor as it occurs in the temperate zones by the following points. (1) Tinea flava begins in childhood and may persist during life. (2) It usually affects the exposed parts of the body. (3) Cure is difficult. (4) The fungus seems to have a marked depigmentary action.

(4) *Endemic vitiligo of Turkestan.*—According to Kistiakovsky, who has observed the disease, there is no difference between this disorder and vitiligo.

(5) *Pinta.*—When this condition is observed early, the characteristic hues of the affected skin in no way suggest tinea versicolor. Later, when vitiliginous areas are present, differentiation may be more difficult. The disease causes coarse scales, the affected skin is infiltrated, occasional fissuring is noted, and loss of hair is usual. When extensively involved, the skin presents an odd, piebald appearance.

(6) *Syphilitic leukoderma.*—This condition is seen almost exclusively in women. The lesions are commonly symmetrically located on the sides and back of the neck, are oval or irregularly shaped and vary from the size of a split pea to that of a dime. Concomitant hyperpigmentation is sometimes noted. No scaling is present. Other evidence of syphilis, including a positive serologic reaction, may usually be detected.

(7) *Vitiligo.*—The irregular, asymmetrical, snow-white patches, showing hyperpigmented edges and affecting by preference the face, hands, forearms and male genitalia, should not often prove difficult to differentiate. No scaling is present. Vitiliginous skin observed under filtered ultraviolet rays has a characteristic fluorescing, glistening white appearance. It must not be forgotten that patients with tinea versicolor may also have vitiligo. This unrelated association is the probable explanation for the absolute achromia reported by a few observers and thought to be consecutive to the pigmented rash of tinea versicolor.

(8) *Posteruptional depigmentations.*—Seemingly depigmented areas may be noted at the former sites of syphilitic, psoriatic and other cutaneous lesions. Without any history of a preceding eruption, differential diagnosis may be difficult.

As with the ordinary form of tinea versicolor, diagnosis requires microscopic studies re-enforced by studies with filtered ultraviolet rays.

(e) PROGNOSIS.—The outlook for complete cure is good if treatment is thorough. Reinfection will occur if the patient is re-exposed, since immunity is not produced by an attack.

(f) TREATMENT.—The extent of the eruption should be determined by a complete examination of the whole cutaneous surface under filtered ultraviolet rays, and the patient should be advised to treat all parts that show fluorescence. If all the affected areas are treated, improvement will be rapid.

It is advisable that all family contacts be examined and, as in the treatment of scabies, that all members affected should concurrently receive therapy. It is important that clothing be cleaned, if possible by washing, although dry cleaning will suffice.

The patient, on examination after two weeks and subsequently, should again be observed under filtered ultraviolet rays. Areas which have escaped medication will be revealed. Scrapings taken from suspected areas will yield either positive or negative information.

We stress the method of treatment rather than the medicaments to be used. A 10 per cent solution of sodium hyposulfite sponged on once daily before the patient retires is a satisfactory application. However, almost any exfoliant or fungicide will prove effective. A hot bath previous to application of the remedy may be helpful.

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8. ERYTHRASMA

This is a superficial mycosis resembling tinea versicolor but with more tendency to localization. Burckhardt first described the disease in 1859.

(a) ETIOLOGY.—The causative fungus is a minute threadlike microorganism, Actinomyces minutissimus (M. minutissimum). Little is known

FIG. 52. Erythrasma. The process is usually localized and well demarcated. *A*, in and near the axilla. *B*, region of umbilicus. *C*, upper inner thighs and inguinal region

concerning predisposing causes or methods of transmission of the infection. Lack of cleanliness may be a factor. The disease is less common in the United States than in Europe. It is seen much less frequently than tinea versicolor.

(b) SYMPTOMS.—The patients are usually young adults, men more commonly than women. There is usually localization to the axillae, the groins, the intergluteal cleft or other intertriginous areas, with involvement of one or more regions. The disease begins as small scaly macules which gradually enlarge to form various sized patches. The lesions are well circumscribed, the margins being accentuated by a reddened border. The color varies through yellowish brown, orange and reddish brown, the exact shade depending on the amount of pigment in the skin of the subject, the age of the lesion (the older the darker) and the amount of solar radiation to which the lesions have been subjected. The surface of the lesions is scaly. Vesicles, papules and follicular lesions are not present.

(c) DIFFERENTIAL DIAGNOSIS.—In tinea versicolor, there is less tendency to localization in intertriginous areas and there is no erythematous border. When the inner surfaces of the thighs, the inguinal region or the pubic area is affected, tinea cruris may be simulated. The long duration, the lack of inflammation (especially of a vesicular border) and the absence of satellite lesions tend to rule out tinea cruris.

The demonstration of the micro-organism may be difficult when one uses the usual technic in examining scales. The organism may sometimes be noted under the ordinary high power magnification, but use of the oil immersion objective is usually requisite in order that one may be certain of its presence. In all cases, a mycologic diagnosis should be made.

(d) PROGNOSIS.—Provided all areas are treated, relapse is uncommon.

(e) FILTERED ULTRAVIOLET RADIATION.—When examined under filtered ultraviolet rays, the eruption shows little change from its usual appearance except that the color is less distinct.

(f) TREATMENT.—All areas of infection as noted by a thorough inspection must be treated. All the affected members of the family should receive treatment at the same time. The daily application of a 10 per cent solution of sodium hyposulfite usually is sufficient. Daily bathing should be carried out to prevent reinfection.

9. TINEA IMBRICATA

This superficial fungous disease is rarely seen except in the tropics or subtropics. It was first recognized and described by Alibert in 1832.

(a) ETIOLOGY.—The causative fungus has been described by Castellani

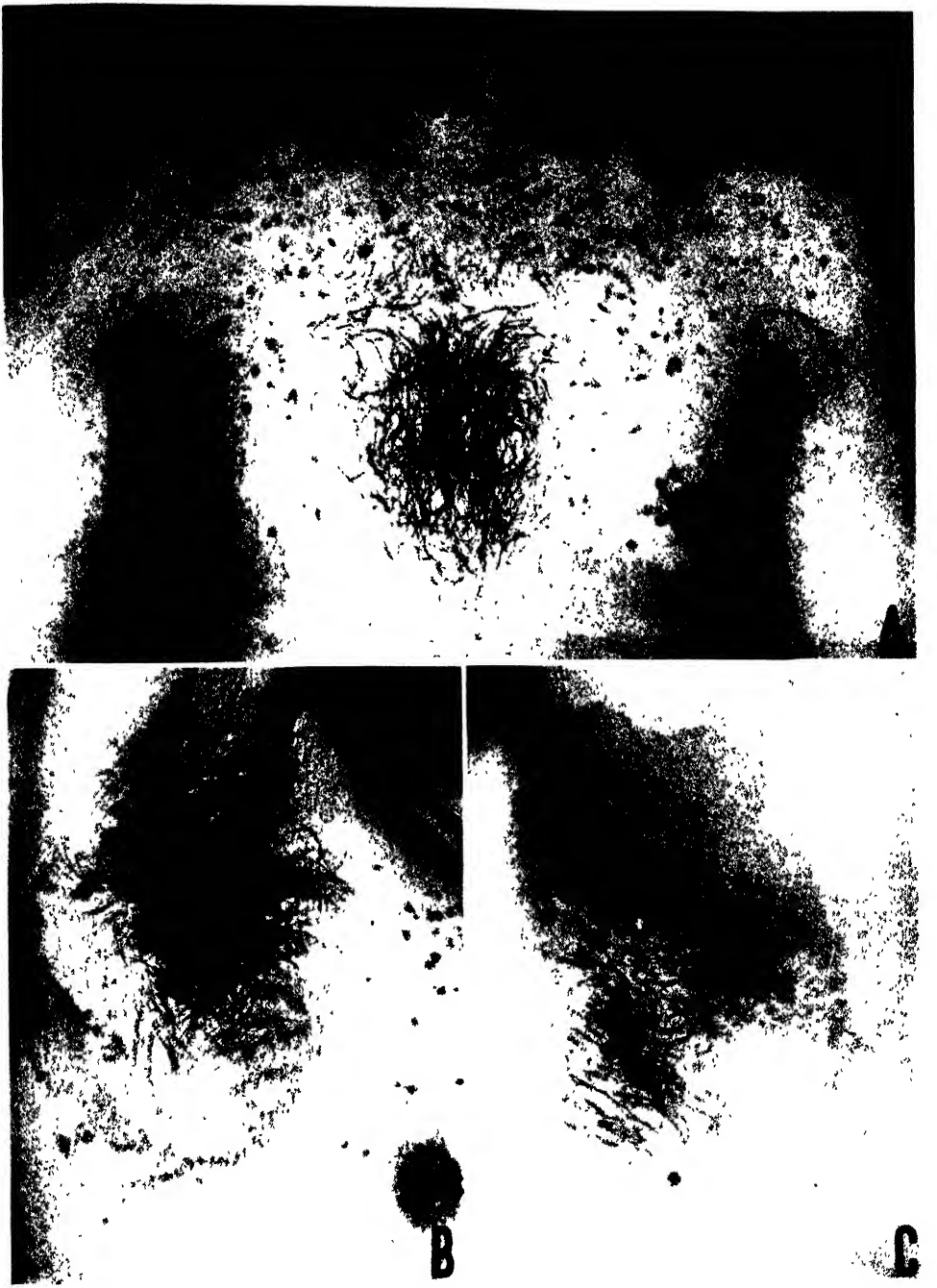

FIG. 53. Erythrasma. *A*, patient with lesions of both erythrasma and tinea versicolor. The lesions scattered over the chest are those of tinea versicolor. *B*, the patient shown in *A*, with lesions of erythrasma in the axilla. *C*, typical site and appearance of a patch of erythrasma.

as belonging to the genus Endodermophyton. He has found four species of Endodermophyta—concentricum, indicum, tropicale and mansoni—to be the pathogens responsible. Most workers believe that these are variants of a single species and classify it as Trichophyton.

Young adults are especially likely to contract the disease, and men are more susceptible than women. Children are less prone to develop tinea imbricata. The condition is observed in places where the coconut tree grows. It is fairly common in many of the Pacific islands, in the Malay States and in central and southern China; cases have also been reported from North China. In recent years it has spread to Ceylon and Southern India. Cases have been reported from South Africa and from South and Central America, but some doubt has been expressed as to their being true instances of tinea imbricata (Castellani).

(b) CLINICAL CHARACTERISTICS.—The condition begins as one or more brownish spots, which slowly increase in size. The central portion of the superficial epidermis finally becomes detached, the epidermis cracks, and there is an opening from the center toward the border. Around the lesion a brownish zone appears. In this latter site, rupture of the skin again occurs. This process is repeated until numerous rings are formed, more or less concentrically arranged and imbricated. Other patches develop, and after several months a large portion of the cutaneous surface may be affected. There is little if any visible redness. Scaling may be profuse. Itching is usually intense. The face is often affected. The scalp also may be involved, but the hair follicles are usually spared. The nails may be infected.

(c) DIFFERENTIAL DIAGNOSIS.—The absence of redness and the typical concentric rings are evidence against the diagnosis of tinea glabrosa. In a case reported by Kittredge an eruption similar to tinea imbricata was caused by T. purpureum. Ichthyosis is usually present from birth, and the scaling lacks the concentric rings seen in tinea imbricata.

(d) PROGNOSIS.—Cure is said to be difficult, and relapse is common.

(e) TREATMENT.—Castellani advised treatment either with 25 per cent resorcinol in tincture of benzoin or with 5 to 10 per cent chrysarobin in an ointment base.

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10. OTOMYCOSIS (MYRINGOMYCOSIS)

This rash of the external ear and the aural canal has a mixed and disputed etiology; it is marked by an exudative inflammation and pruritus.

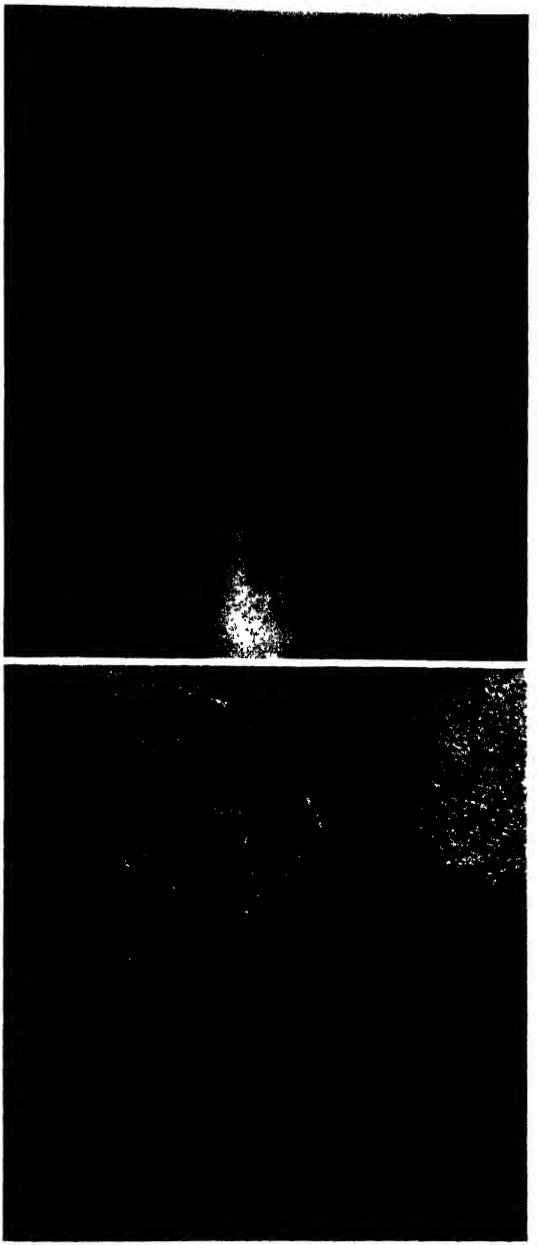

FIG. 54. Tinea imbricata in a Chinese. *Above*, irregular gyrate patches on the legs. *Below*, the elevated border and tendency to concentric scaling shown with magnification. (*Courtesy of Frederick Reiss.*)

(a) ETIOLOGY.—While a number of writers have described this disorder as of fungous origin, few exact technical studies have been carried out. Whalen stated that species of Monilia, Aspergillus, Penicillium and Achorion may be found. He mentioned that in China and in the Americas the predominating organism is a species of Aspergillus. In the Canal Zone, however, Monilia is more often found. The question arises whether these fungi, which are for the most part common laboratory "tramps" and may be cultured from the surface of normal skin, can be incriminated as the cause of the disease in question. The evidence so far offered is not sufficient to prove beyond doubt that they can. It is possible that the special conditions present in the external aural canal, particularly with retained cerumen, also favor the proliferation of ordinary saprophytes, so that a pathogenic propensity is established. In our studies, Aspergillus has been a common finding, but autoinoculation experiments on several occasions have not been successful. If a species of Aspergillus is to be considered pathogenic, it must be with the qualification that the site and the material present are predisposing factors. We have cultured few fungi of recognized pathogenic titer from this site. Streptococci have also been considered as possible causative agents, since they are sometimes obtained on culture. We have not noticed a common history of allergy in patients with otomycosis. No age is exempt, although the majority of patients are young adults. Season and climate have little effect on the course of the disorder. Swimming in infected pools has been suggested as the origin of some characteristic infections.

(b) SYMPTOMS.—The external ear around the meatus is swollen and red. A moist mass of débris is usually present and may completely fill the canal. When this is removed, the affected skin is seen to be exudative. If the condition is mild or just beginning, the débris may be scanty, and at times it is dry and flaky. While pruritus (worse at night) is present in almost every case, evidence of trauma is rare. The disorder may extend down the canal and affect the drum. It has been said that if the drum is perforated, the infection may extend to the tympanic cavity and even invade the mastoid cells.

(c) DIFFERENTIAL DIAGNOSIS.—Seborrheic eczema is rarely observed in this site alone, so evidence should be sought on the scalp, behind the ears and in other sites. The crusting has an oily character not present in otomycosis.

We are unable to differentiate this disorder from the exudative inflammatory disorder due to streptococci described by Mitchell as occurring on the infra-auricular fold.

Localized atopic eczema is of frequent occurrence and in this location

may predispose to invasion by micro-organisms. With this disorder there are usually an associated family or personal history of other allergic diseases and a discernible allergen to account for the exposure; change of environment or season should favorably affect the disease if uncomplicated by micro-organisms. Contact dermatitis from nail polish, hair lotion or dressing, or other skin sensitizing agents is usually seen in women, is very pruritic and often affects the eyelids.

(d) PROGNOSIS.—Treatment is usually successful, although recurrence is not uncommon.

(e) TREATMENT.—The extent of the disease should be ascertained. If it is localized to the external ear and the aural canal (the usual sites), the following treatment may be given.

1. Irrigate with a warm dilute solution of sodium bicarbonate until all the débris is removed.

2. Paint the affected area with a 1 per cent aqueous solution of gentian violet. Other drugs which may be painted on include a 1 per cent aqueous solution of brilliant green, a 1 per cent solution of silver nitrate, 2 per cent salicylic acid in alcohol, 5 per cent phenol in glycerin and 1 per cent thymol in alcohol.

3. Roentgen rays in fractional dosage are often valuable, administered either alone or in combination with one of the remedies just mentioned.

4. Acetylsalicylic acid, given internally, is useful to relieve the pruritus.

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11. LEPOTHRIX (TRICHOMYCOSIS AXILLARIS)

This is a common silent disorder in which nodes develop on the axillary hair.

(a) ETIOLOGY.—According to Castellani, Actinomyces tenuis is the causal micro-organism. Micrococci may be associated and are said to be responsible for the formation of red or black pigment if present. Huang isolated A. tenuis in 24 of 25 instances of the disorder.

(b) CLINICAL CHARACTERISTICS.—The condition is noted in the axillae, where irregular concretions form and attach themselves to the hair. Occasionally the pubic hair is affected. The attachment is firm, and the nodes are difficult to dislodge. The entire circumference of the hair is ordinarily involved. The concretion is usually yellowish; red and black varieties are uncommon in New York but are seen with more frequency in the tropics.

Hairs on which the nodosities form may become friable but are otherwise unchanged. Weidman cultured a species of Actinomyces from a hairy black tongue. When the fungus was fed to a monkey, lesions of trichomycosis developed on the hair of the face and of the axillae.

(c) DIAGNOSIS.—This is usually indicated by the clinical appearance. The concretions, or nodes, exhibit fluorescence under filtered ultraviolet rays. If a hair to which the concretions are attached is examined under a microscope, the mass is seen to be present along a portion of the hair and nits can be excluded from consideration. In our experience, microscopic and cultural examinations have been fruitless so far as the demonstration of fungi has been concerned. Special mediums are necessary, such as those used in isolating Actinomyces bovis.

(d) TREATMENT.—The daily use of 10 per cent xylene in petrolatum sometimes dissolves the concretions. Shaving the part is the fastest and surest cure. Recurrence is common. Scrupulous cleanliness is essential to prevent recurrence.

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12. TINEA NODOSA (PIEDRA)

According to McCarthy, two varieties of this disorder exist: (1) the Colombian (South American) type, and (2) the European and Asiatic variety. In both, the disease is manifested by small, hard nodes along the involved hair shaft. We have not observed this disease in New York.

(a) ETIOLOGY.—The disease is said to develop in individuals who wash their hair in stagnant river water and then apply a sticky hair dressing. Two fungi, Trichosporum (Piedraia) hortai and Trichosporum giganteum, are causative. The first-named micro-organism may be isolated from black nodes, whereas the latter is credited as the etiologic agent in the so-called "white" variety in which the nodes are light brown. The infective agent may be demonstrated by mounting the hair with nodes attached in potash solution. The hair is said not to be affected in any way. According to McCarthy, the nodes are made up of a large number of closely packed cells.

(b) CLINICAL CHARACTERISTICS.—The disease is confined to scalp hair of women in South America. The European and Asiatic variety affects only the male beard and mustache, never the scalp. The nodules of both varieties are stony hard and light or dark brown. In the Colombian variety they may be so small that they can be felt but not readily seen; in the other type, the nodules are usually large enough to be seen. From one to 25 may be present on one hair.

(c) DIAGNOSIS.—The color and location of the nodes are different from those of lepothrix, which are yellow or red and confined to the axillae. Nits project out typically, are accompanied by pruritus, and pediculi may usually be found. Monilethrix and trichorrhexis nodosa may be simulated, but these diseases are readily distinguished if the hair is examined microscopically.

(d) TREATMENT.—Shaving is a certain cure. Vigorous shampooing and the application of 1:2,000 solution of bichloride of mercury are also advocated.

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13. CHROMOBLASTOMYCOSIS (DERMATITIS VERRUCOSA)

For the few cases that have been reported, there is a remarkably wide geographic range. In the United States, cases have been reported from Boston, Texas, North Carolina, Georgia, St. Louis, Philadelphia and Florida. The majority of cases have been recognized in South America, Puerto Rico and Cuba. An instance of an infection in the Dominican Republic was reported by Carrión and Pimentel-Imbert. According to Conant *et al.*, it has also been observed in Russia, Japan and South Africa.

(a) ETIOLOGY.—According to Carrión, three fungi are recognized as causative. Both he and Emmons stated the belief that there is a generic relation between them. The fungi are Hormodendrum pedrosoi, Hormodendrum compactum and Phialophora verrucosa. Conant and Martin also included Hormodendrum langeroni as a proved cause. According to Weidman, infection usually takes a direct route from the exterior following injury, particularly from wood. Most patients are mature males, predominantly of the working class.

(b) IMMUNOLOGIC REACTIONS.—Conant and Martin noted that the serums of rabbits immunized with H. pedrosoi and H. compactum had a high titer of complement-fixing antibodies for their respective antigens and for each other. With P. verrucosa and H. langeroni, complement-fixing bodies were present only for the homologous fungus.

FIG. 55. Chromoblastomycosis; superficial papillomatous lesions of several years' duration. (*Courtesy of A. L. Carrión, San Juan, Puerto Rico.*)

(c) SYMPTOMS.—There may be a superficial resemblance to tuberculosis verrucosa cutis or to blastomycosis. The lesions usually develop on the leg; the condition may begin as a verrucous nodule or an ulcer. The nodule may be reddish, purplish or brownish. After many months or years, verrucous masses may result from coalescence of two or more lesions and their subsequent growth. Pruritus may or may not be present. In Lane's case there were two lesions, one an ulcer and the other a nodule, both on a buttock. Later, large cauliflower-like masses may be noted, with secondary invasion of saprophytic micro-organisms, and a foul discharge may be present. No instance of metastasis to an internal organ has been recorded; rarely, subcutaneous or intramuscular lesions occur at sites remote from the original focus of disease. Edema of the foot and ankle is frequent. Adenopathy is infrequent. In the case of chromoblastomycosis reported by Carrión as due to H. compactum, the lesions were on the left arm and of 28 years' duration. There were no ulcers or large warty or cauliflower-like lesions. The eruption spread by extension rather than by satellite lesions, as is usual. The rash was dry, dull red or violaceous and scaly and was well demarcated. Scarring was present in healed areas. The disease resembled psoriasis, lupus erythematosus and tuberculosis.

(d) HISTOLOGY.—According to Weidman, the tissue reaction consists of granulomatous changes similar to those resulting from the presence of a foreign body; there are also interspersed small foci showing a tuberculoid reaction and still other areas in which there is some miliary abscess formation.

(e) DIFFERENTIAL DIAGNOSIS.—Blastomycosis and tuberculosis verrucosa cutis may be confused with chromoblastomycosis. In blastomycosis the flat border studded with pustules and the budding of the organism in pus are two prominent differences, but with tuberculosis verrucosa cutis, only the results of mycologic study and the results of inoculation of guinea-pigs may serve as distinguishing features.

(f) PROGNOSIS.—While there is no tendency to spontaneous recovery, the prospect for cure is good. There is no need to fear internal involvement.

(g) TREATMENT.—The administration of potassium iodide by mouth or sodium iodide by intravenous injection has proved curative in a number of instances. While we have had no experience in treating the disorder, roentgen therapy appears to be indicated, since it is effective in disorders of somewhat similar pathologic characteristics. Conant *et al.* treated one patient with copper sulfate administered by means of iontophoresis and obtained a good result after five months. If the condition is localized, electrodesiccation and curettage should be successful.

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CHAPTER X

The Deep Mycoses (Essentially or Potentially Systemic)

DURING a lifetime of work in private and hospital practice, a physician may see only a few patients with one of the deep fungous infections. However, the prompt recognition of the disease is vitally important, since delay in beginning treatment may result in a fatal outcome. Patients suffering from these rare yet potentially dangerous diseases may consult the general practitioner, the internist, the surgeon, the gynecologist or some other specialist as well as the dermatologist; thus consideration of a few essential facts concerning the detection and management of these diseases appears of general interest. As a rule, diagnosis of the deep mycoses is not difficult, if they are kept in mind as possibilities. The following will be discussed:

1. Actinomycosis (streptothricosis)
2. Mycetoma (maduromycosis)
3. Nocardiosis (actinomycosis without granules)
4. Sporotrichosis
5. Blastomycosis
6. Histoplasmosis
7. Coccidioidomycosis
8. Granuloma paracoccidioides
9. Torulosis
10. Rhinosporidiosis
11. Aspergillosis
12. Mycoses of the lungs

1. ACTINOMYCOSIS (STREPTOTHRICOSIS)

Of all the rare, deep mycoses, this is probably the most widely distributed throughout the world. It may remain in a localized stage, in which

vigorous treatment is curative, or become generalized in extent, when it may cause the death of its host. The disorder was described and named by Bollinger, while in the same year (1877) Harz named the organism producing the disease, A. bovis. This organism was first cultured and carefully studied by Wolff and Israel. Bostroem found the fungus in diseased cattle. Murphy and Ruhräh first reported the disease in the United States. Blain estimated that about 1,000 cases of actinomycosis have been reported in this country and concluded that the actual number of cases in the population is many times as great.

(a) INCUBATION PERIOD.—This is not definitely known, but it is probably only a few days or weeks.

(b) ETIOLOGY.—Several fungi have been considered as the causative organisms. It is generally agreed now that in many if not all cases actinomycosis proper is caused by A. bovis (Harz; Wolff, and Israel). The disease is more prevalent in farming country than in urban districts; nearly half the patients suffering from this disease are engaged in agricultural pursuits. Wild and domestic animals (particularly cattle) are susceptible to the infection. However, inoculation of cultural material of A. bovis into animals never completely reproduces the disease. In half the cases no infection results, and even when inoculation is successful only insignificant lesions appear. Adults are affected more commonly than children and males much more often than females (approximately 2:1). Actinomycosis bovis has been isolated from the normal mouth and throat and is probably frequently present in the mouth, throat and gastrointestinal tract of healthy human beings and animals. Emmons found granules containing Actinomyces in 47 per cent of the tonsillar crypts in a series of 100 consecutive tonsillectomies; in approximately half of these, a growth was obtained of a microaerophilic Actinomyces considered to be A. bovis. Trauma is undoubtedly a frequent precipitating factor, and cases of infection following extraction of teeth and resulting from bites are not uncommon. There is a possibility that the saliva and the nasal discharges may also be responsible for its transmission.

(c) CLINICAL CHARACTERISTICS.—According to Steinbach, the disease in human beings has four anatomic localizations: (1) head and neck, 50 per cent; (2) abdominal organs, 20 per cent; (3) thoracic organs, 15 per cent, and (4) other organs, including the skin, 15 per cent. Cope's statistics are in virtual agreement. The infection may spread by continuity or by means of the blood stream to involve any part of the body.

(*1*) *Head and neck.*—The primary lesion may often be detected in the buccal mucous membrane. The gums, the tonsillar crypts or other parts of the mouth may be involved, the infection traveling to the subcutaneous

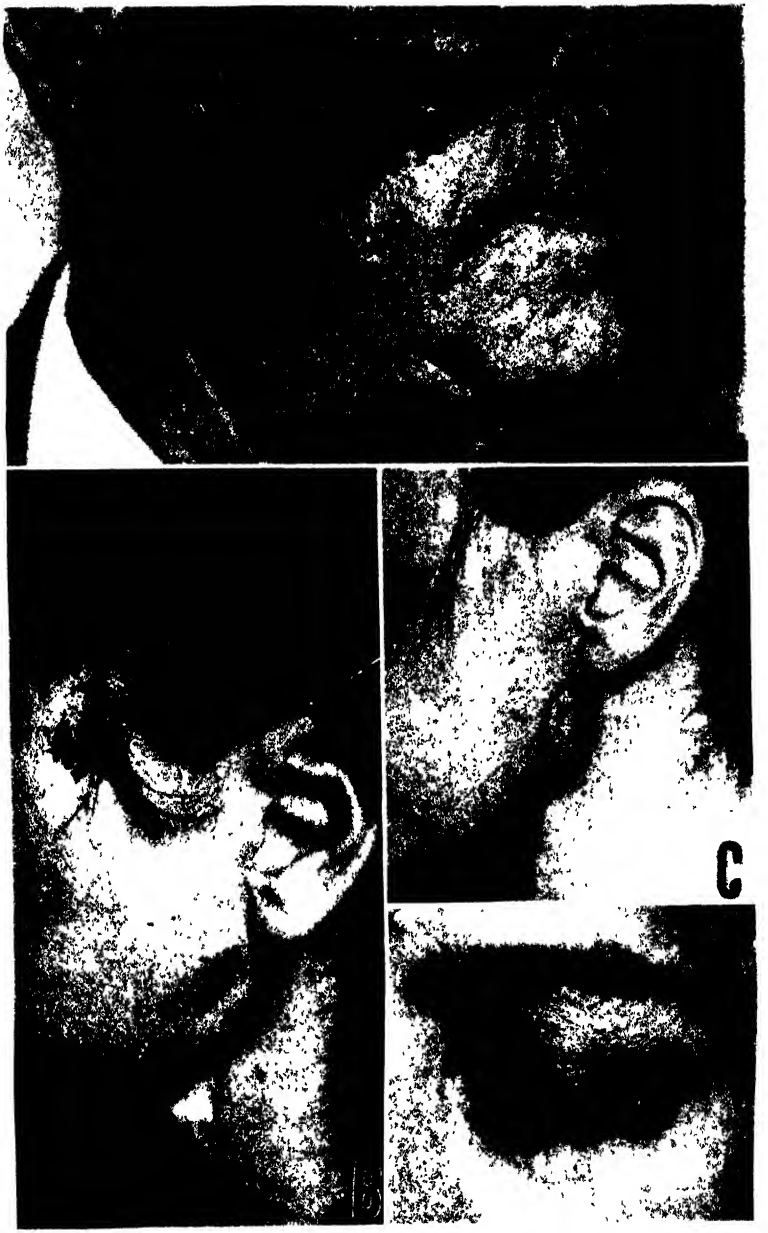

FIG. 56. Actinomycosis. *A*, infection which, beginning in the region of the parotid gland, burrowed under the skin to affect a large portion of the right cheek. Some of the scars are the result of variola; this patient also had a laryngeal carcinoma, which was apparently cured by surgical excision. As seen in *B*, the openings of the sinus tracts exuded pus containing white flecks. These on microscopic examination revealed the ray fungus. *C*, the patient seen in *B*, showing successful results from local use of roentgen rays and internal administration of potassium iodide. *D*, solitary lesion opening on the lower eyelid.

tissue, where nodules develop. These nodules increase in size, suppuration takes place, and pus is discharged to the surface of the skin. Sinus tracts then develop. The infection may slowly progress subcutaneously, with the same sequence of events, until considerable areas of skin are involved. A variable degree of edema may be noted. The tissues in the affected regions are usually bound down and often have a boardlike consistency. Pus usually may be expressed from the sinus openings. In the pus, the organism may be found in the form of granules (yellowish or white flakes). Sometimes these granules are not grossly noticeable unless the pus is spread out on a slide. The mandible and other bones, the parotid gland, the nose, the eye and the tongue have all been found capable of being infected.

(2) *Abdominal organs.*—The disease usually begins in the appendix or cecum; in women, the fallopian tubes may be primarily involved. The disease may also attack the gallbladder and the liver, producing abscesses. The symptoms of involvement in the abdomen usually result in operations, when the disease may or may not be suspected. The operation wound refuses to heal, and sinuses discharging pus remain. Spontaneous sinus formation before operation is unusual. An instance of primary actinomycosis of the stomach with metastasis to the liver was reported by Blain.

(3) *Thoracic organs.*—The involvement may be primary, or it may be secondary to buccal actinomycosis. Tuberculosis with cavitation may be markedly simulated; chronic bronchitis and pneumonia, more rarely. Carcinoma is occasionally difficult to differentiate. There is discharge of pus in the sputum. Pain because of pleuritis is a common symptom. The lower lobes of the lungs are usually involved. The infection almost always spreads to the chest wall, with the production of sinuses to the exterior. If untreated, the patient develops a septic temperature, loses weight, and secondary infection often supervenes.

(4) *Other organs.*—Primary cutaneous involvement is rare; when it does occur, ulcerations form, and the infection gradually becomes deeper. According to Jacobson, only 13 cases of primary actinomycosis of the kidney have been reported, involvement of the urinary tract being more often secondary to infection of other parts. Cerebrospinal involvement has been reported; it is probably always secondary. The symptoms are either those of an acute infection or those of a neoplasm. Besides the bones of the face, previously mentioned, the vertebral column is occasionally involved secondarily to an intestinal or pulmonary infection.

(d) Histology.—The morbid picture is essentially the same no matter what tissue or organ is affected. At an early stage colonies of fungi are noted in the center of the lesion, together with polymorphonuclear leuko-

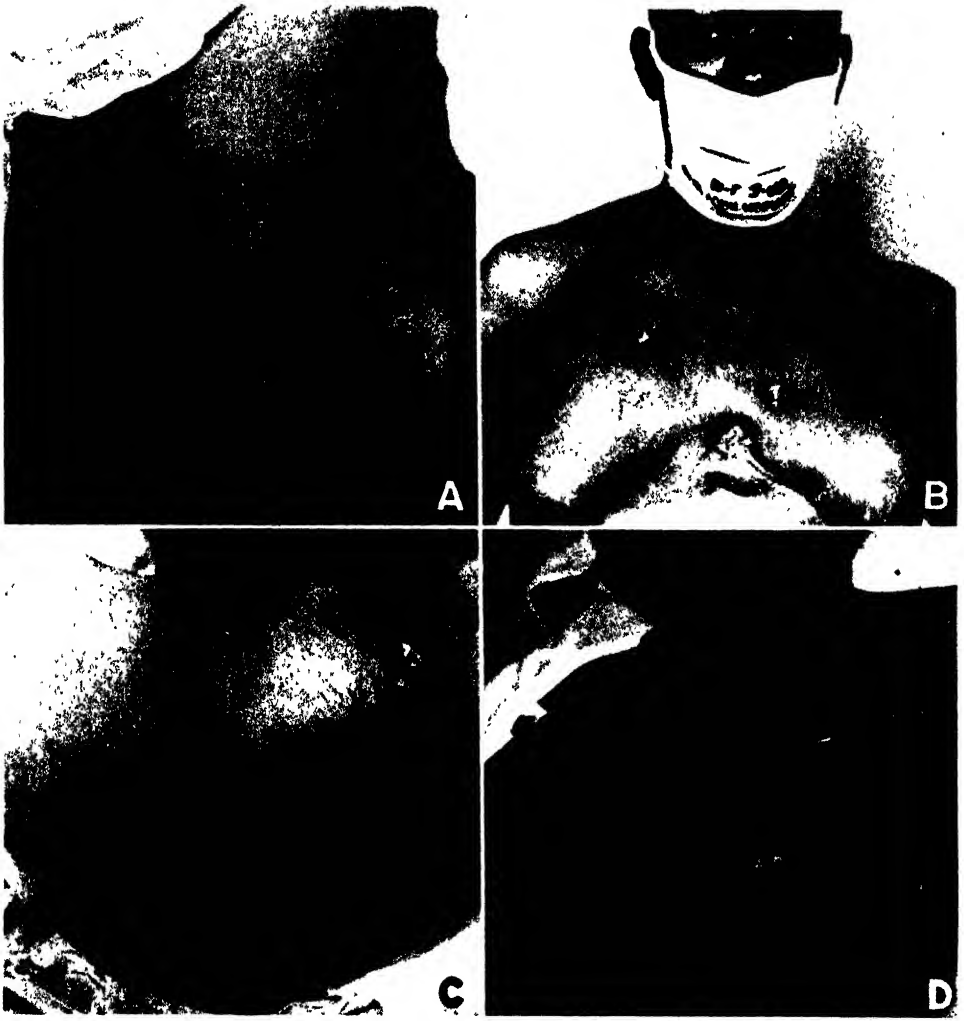

FIG. 57. Actinomycosis. Sinus tracts leading to visceral lesions. *A* and *B*, patient from Afghanistan with intestinal fistulas, in pus from which granules were readily demonstrated. *C* and *D*, pleural and subcutaneous sinus tracts. Both patients responded well to therapy with penicillin and sulfonamides.

cytes, lymphocytes, plasma cells and eosinophils. Surrounding them is a variable amount of cellular detritus and granulation tissue. The ray fungus is described further on pages 320 and 323. As the lesion increases in size, the central purulent area becomes larger, and finally the pus pushes through normal tissue. Granulation tissue or, in later stages, scar tissue may be the only pathologic finding and granules may not be found. The final outcome is the development of sinus tracts leading to the surface of the skin or to a cavity within the body.

(e) IMMUNE REACTIONS.—It was shown by Colebrook that serum taken from a patient with the disease will agglutinate the causal micro-organism. The diagnostic value of cutaneous tests with vaccines has been appraised by Conant *et al.* who reported that patients with actinomycosis are sensitive to both intracutaneous and subcutaneous injections of a vaccine made from the causative organism.

(f) DIFFERENTIAL DIAGNOSIS.—While the absolute diagnosis rests on the demonstration of the ray fungus in the pus (see pp. 320 ff.), the clinical picture is usually highly suggestive. The location, the development of sinus tracts and the presence of white or yellow granules in the pus are characteristics rarely noted with other infections. Sporotrichosis may be differentiated by the absence of granules in the discharge, by the development of successive lesions along a lymphatic chain and by breaking down of the lesions into ulcerations. Sporotrichum schencki is readily cultured but not demonstrated in pus. Granuloma coccidioides is characterized by the development of soft granulomatous lesions on various parts of the body, with symptoms of systemic infection. Coccidioides immitis is present in the pus, and guinea-pigs readily become infected. Tuberculosis may be simulated in lesions in the skin, in the lungs and in the vertebrae. Finding the ray fungus is necessary to determine the diagnosis; cultures of sputum which yield Actinomyces may be misleading, since the fungus is frequently saprophytic in the mouth. The roentgen picture of the lungs usually shows the disease affecting the lower lobes and rarely reveals cavity formation. When the vertebral column is affected, tuberculosis is simulated, but tuberculosis is usually limited to the anterior portion of the vertebral bodies. With involvement of the abdominal viscera, the diagnosis will be determined if actinomycosis is kept in mind as a possible cause for persistent sinuses following operation and if wet preparations of material from unusual pustular conditions found at operation are made routinely and examined for the ray fungus. When the tongue alone is involved, syphilis, carcinoma, tuberculosis or pyoderma may be suspected until the ray fungus is demonstrated. An elevated sedimentation rate and a moderate leukocytosis may occasionally be helpful laboratory findings.

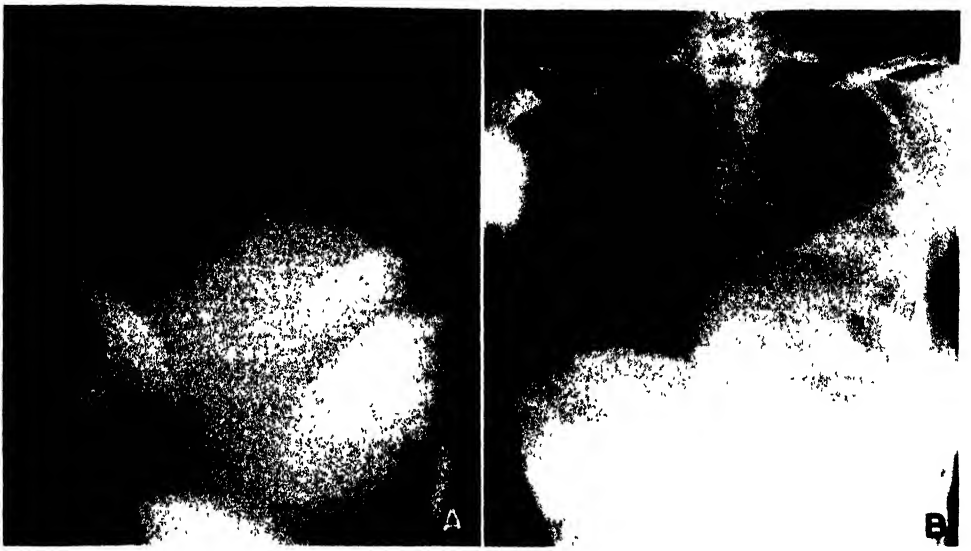

FIG. 58. Actinomycosis of the chest as shown by roentgenograms. *A*, infiltration in right lower lobe with associated pleural effusion; generalized cardiac enlargement. In the lateral view, the patchy infiltration was seen to occupy the right middle and lower lobes. *B*, symmetrical thorax with smooth high diaphragm on the right. The diaphragm on the left is in average position but shows tenting. Both costophrenic angles are clear. Size and shape of heart shadow are not unusual. The right lower lobe is reduced in volume and the lung markings are prominent in this region. The dense shadow in the hilar region is probably due to an enlarged lymph node. In the third left interspace, a uniform density is noted which gradually fades out toward the second anterior interspace. The first interspace is entirely clear. There is a veil-like density throughout the lower left lung field. In the lateral film, a dense round shadow, probably an enlarged lymph node, was seen in the hilar region.

(g) PROGNOSIS.—When localized, the disease usually responds well to treatment. In the systemic varieties, the issue is doubtful but not hopeless unless the brain and the spinal cord become affected. The period of involvement is important; infections of long duration are of graver portent than those of recent origin. The prognosis also depends on the nature of the treatment and on the efficiency with which it is carried out. The virulence of the infection may vary, and the natural immunity of the host also seems to be of importance in many cases.

(h) TREATMENT.—This should be undertaken as soon as the ray fungus has been demonstrated in pus. Even when the outlook is favorable, progress is slow and several months are required for cure. The following measures are usually employed.

(*1*) *Preferred.*—Combined therapy using penicillin, sulfadiazine and roentgen irradiation is advocated by Lamb and others and appears at this time to be superior to other schemes. It is recommended in all forms of the disease.

A. Penicillin. This drug should be given intramuscularly, 40,000 units every three hours to a total dose of at least 6,000,000 units.

B. Sulfadiazine. In 1938, Walker reported favorable results from the administration of sulfanilamide. There has since been ample evidence that the sulfonamides are useful agents. We prefer sulfadiazine because of its low toxicity. The dose at first should be from 4 to 6 Gm. daily, reduced to 2 Gm. daily after clinical improvement. Sodium bicarbonate should be prescribed to be taken coincidentally. It may be necessary to continue sulfonamide therapy for two to three months. The urine and blood should be examined regularly.

C. Roentgen rays. This is usually administered to accessible lesions in semi-intensive dosage with some filtration. The treatment should be repeated at intervals of three or four weeks. In cases of systemic infection, high voltage therapy usually results in symptomatic relief.

(*2*) *Other measures.*

A. Iodides. It is customary to use a saturated solution of potassium iodide, first giving 10 drops three times daily before meals in a glass of water. The dose may be increased 5 drops each day until symptoms of intolerance develop. Patients with actinomycosis appear to have more than average tolerance for iodides, and large doses (up to 200 to 300 drops or more per day) are frequently well tolerated. Tincture of iodine may be given instead of potassium iodide, and other forms of iodide medication may be substituted to provide a change for the patient during the long course of treatment. It is usually necessary to continue the administration of the iodides for several months.

B. Copper sulfate. This is of dubious value; ¼ gr. (0.016 Gm.) may be given by mouth, or colloidal copper may be administered intravenously.

C. Local treatment. This should consist of irrigation of the sinuses with compound solution of iodine (Lugol's solution), diluted, or with a 1 per cent aqueous solution of gentian violet. Packing the sinus tracts with formaldehyde gauze has also been advocated.

D. Surgical intervention. Accessible lesions may be completely excised or incised to provide irrigation.

E. Thymol. Preliminary experiments by Myers showed that a 1:1,000 aqueous solution of thymol possesses the power of destroying Actinomyces in 45 seconds. Myers treated five patients with thymol locally and systemically, and all recovered. A patient who refused to take thymol internally died of visceral involvement. For local use, Myers used a 10 to 20 per cent solution of thymol in olive oil. For internal use, thymol was administered by mouth in crystal form in 1 or 2 Gm. capsules once daily or less frequently. It was given on an empty stomach. While the small number of patients who have been treated with thymol does not allow fair evaluation of its worth, we are of the opinion that it has merit and may be used for patients intolerant to the drugs advocated in the preferred schedule.

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2. MYCETOMA (MADUROMYCOSIS)

In this disease, caused by any one of several species of Actinomyces and by other genera, there is deep destruction of a member, usually a foot, with the development of sinus tracts. Over 35 authentic cases have been recorded in this country.

(a) ETIOLOGY.—The disorder is seen in endemic form in India, especially in Madura. It is more common in males than in females. Persons of all ages are vulnerable, but it is rarely seen before puberty. It is more common in those who are barefoot while working in the fields. Injury in the form of an abrasion may be requisite to introduce the infection.

A number of fungi other than Actinomyces have been described as capable of causing the disease. Although we have had only limited personal experience, it seems that the causative fungus is often difficult to grow on artificial mediums. Many of the fungi described as pathogenic may merely be growing saprophytically in the diseased tissues.

The subject has been reviewed by Gammel and others. The reader is referred to the articles mentioned in the bibliography for further enlightenment on this greatly confused subject.

(b) CLINICAL SYMPTOMS.—The disease is first manifested by a subcutaneous swelling. This may become phlegmonous and rupture to the cutaneous surface. Sinus tracts form, and the infective process burrows into the deeper structures of the foot, which becomes swollen and distorted. On the surface are numerous pea-sized eminences; in the center of each is the orifice of a sinus. The discharge is seropurulent and contains rounded white, yellowish, reddish or blackish granules. The disorder progresses slowly and may last for 30 years (Crocker). The usual period before the patient is incapacitated is from three to seven years. The tumor may become very large, increasing the bulk of the foot to four or five times the normal size. Usually, the destructive process finally involves the small bones. Rarely, some other part of the body may be the site of the disease; an instance of involvement of the hand was reported in 1940 by Lewis and Sachs. In a later communication (*Journal of Investigative Dermatology*, 10:156, 1948) the condition was classed as chromoblastomycosis.

The disease is solely of local import. Constitutional symptoms are slight, and the internal organs are never involved.

(c) PROGNOSIS.—If treatment is commenced before too much destruction

of the tissues has taken place, a satisfactory result may be expected.

(d) TREATMENT.—The internal administration of iodides and roentgen therapy in filtered dosage comprise the treatment usually employed. Sulfonamide therapy may be effective when the causal micro-organism is a species of Actinomyces. With severe destruction of the tissues, surgical amputation has been necessary.

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3. NOCARDIOSIS (ACTINOMYCOSIS WITHOUT GRANULES)

There are several reported cases of infections of the skin, of the subcutaneous tissues and of the lungs in which Nocardia (a species of Actinomycetaceae which is a common saprophyte of soil) was considered the cause.

Guy summarized the literature and reported a case in which the lesions led to a clinical diagnosis of sporotrichosis. The clinical course and the rapid response to iodide therapy also suggested this diagnosis. The evidence (which included isolation of the fungus in culture and detection of a fine mycelium in histologic section) is not entirely conclusive that the organism isolated (Nocardia) was more than a contaminant. Guy and Helmbold reported a case in which gangrenous sloughing ulcers (clinically suggesting pyoderma gangrenosum) successively developed, and there was associated bloody diarrhea with ulceration of the rectum and sigmoid. In this instance a species of Nocardia was isolated both from the lesions and from the blood stream during a chill. Mycelium was noted in histologic section. Cure followed blood transfusion and intensive iodide therapy. Gammel reported that in a case in which death occurred the causative agent was a species of Actinomyces. Granules were not present. In this case the first lesions were situated in the skin and metastatic lesions in the skin and brain. The micro-organism was repeatedly isolated from open and closed (deep) lesions in the skin. Mycelium was found in the spinal fluid, but the organism did not grow on culture. Lamb observed a man with multiple nodular fistulous lesions of the neck of 15 years' duration. The clinical diagnosis

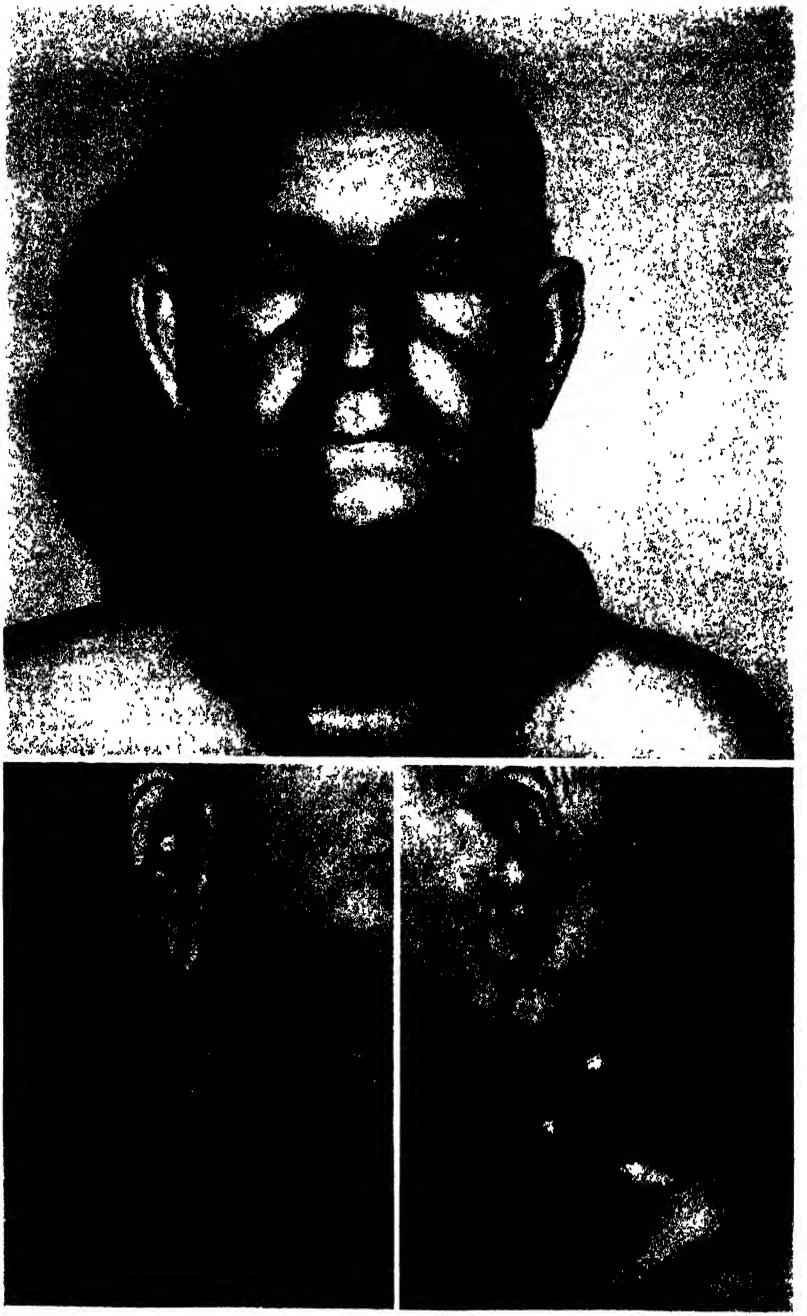

FIG. 59. Nocardiosis (actinomycosis without granules). Infection of 15 years' duration, with large fluctuant masses on the left side of the neck and draining sinuses on the right. No granules could be demonstrated in pus aspirated from unruptured lesions. An aerobic Actinomyces was repeatedly isolated on culture. (*Courtesy of John Lamb.*)

was actinomycosis, but no granules could be found in the pus from an unruptured lesion. There was no difficulty in growing an aerobic Actinomyces.

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4. SPOROTRICHOSIS

While this disease was thought to be more prevalent in France and in the Mississippi Valley than elsewhere, the largest number of cases has been reported from South Africa. Pijper and Pullinger in 1927 described an outbreak of sporotrichosis affecting 14 native miners working in one gold mine. In 1941, Dangerfield and Gear reported 74 cases occurring in workers in two Witwatersrand gold mines. A year later du Toit added 650 cases to the total for South Africa, when he reported an epidemic occurring in a shaft where about 2,500 native workers were employed. Du Toit further mentioned that many other cases had not been recognized in other gold mines and have not been recorded. Schenck in 1898 first described the disease in this country. Smith classed the organism as a member of the genus Sporotrichum. A few more than 200 instances of the infection have been recorded in this country, and only five cases in which the diagnosis was proved have been reported from New York. The reports of de Beurmann, Ruediger, Meyer, Foerster and du Toit may be cited as particularly valuable for reference.

(a) PERIOD OF INCUBATION.—This is usually in the neighborhood of one week. It may vary from three days to three weeks (Dangerfield and Gear).

(b) ETIOLOGY.—While several members of the genus Sporotrichum have been considered of pathogenic significance, S. schencki seems to be of predominant importance in this country. Numerous species of Sporotrichum are common saprophytes, being found on many types of vegetation in all parts of the world. They are also found in the excreta of human and animal carriers. Sporotrichum schencki has been inoculated successfully on carnations (Benham and Kesten), and the work of Foerster indicated that the barberry shrub is of importance as an intermediary host. Sphagnum moss was thought to be the residual focus for the Sporotrichum in cases of six florists (Gastineau, Spolyar and Haynes). There is frequently a report of local injury or trauma with a thorn, cactus or briar. De Beurmann has shown that the organism may permeate the intact intestinal mucosa, and the infection thus may be contracted through the eating of contaminated

raw fruits or vegetables. Sporotrichum schencki is pathogenic for the higher animals such as horses or mules, and some of the lower animals also may acquire lesions of sporotrichosis, the rat being particularly susceptible. In isolated instances the disease has been acquired from the bite of a rat, from patients with the disease and from cultures of the organism.

In the majority of instances in the United States the disease in human beings is probably due to contact with infected vegetation at a site of local injury. The investigations of Dangerfield and Gear and of du Toit have focused attention on another means of dissemination of the disease. Dangerfield and Gear were certain that the infection in workers in gold mines in South Africa was contracted underground, but attempts to culture the fungus from rock, timber and underground water were unsuccessful. Rats caught in the mine were likewise not infected. Du Toit was more successful and isolated a Sporotrichum from dust floating about in the air and from timber, on which it was growing profusely. He was not certain that this fungus was the agent causing sporotrichosis since it was less virulent when rats were inoculated and the disease could not be produced when the fungus was injected into human volunteers.

(c) CLINICAL CHARACTERISTICS.—There are a number of clinical types of the disease. These may be summarized as follows.

(*1*) *Localized lymphangitic type.*—Most of the reported cases in South Africa and in the United States are of this variety, in which a primary lesion, or chancre, appears on an exposed part of the body. The usual site is a finger or hand. In two recent cases, one of which was presented by John C. Graham, the initial lesion was on the face. The primary lesion is indurated; softening and abscess formation may take place; an indolent ulcer may develop, or the lesion may vegetate. Rarely the disease remains localized to this single lesion. Usually after a week or more a painless ascending inflammation develops in the regional lymphatics, along the course of which secondary nodules form and undergo changes similar to those noted in the chancre. Enlargement of regional lymph nodes is uncommon (an important diagnostic point in the clinical differentiation from tularemia, in which enlargement of lymph nodes is a constant finding). Systemic symptoms and generalized involvement are uncommon. There is little if any tendency to spontaneous recovery. Scarring of varying degrees of severity remains after involution of the lesions.

(*2*) *Disseminated subcutaneous type.*—In this variety, commonly observed in France, small hard painless subcutaneous nodules of varying number appear in scattered locations over the body. Within three to six weeks the skin becomes involved; the central part of the nodule softens and forms an abscess which may discharge if traumatized, becoming a cup-

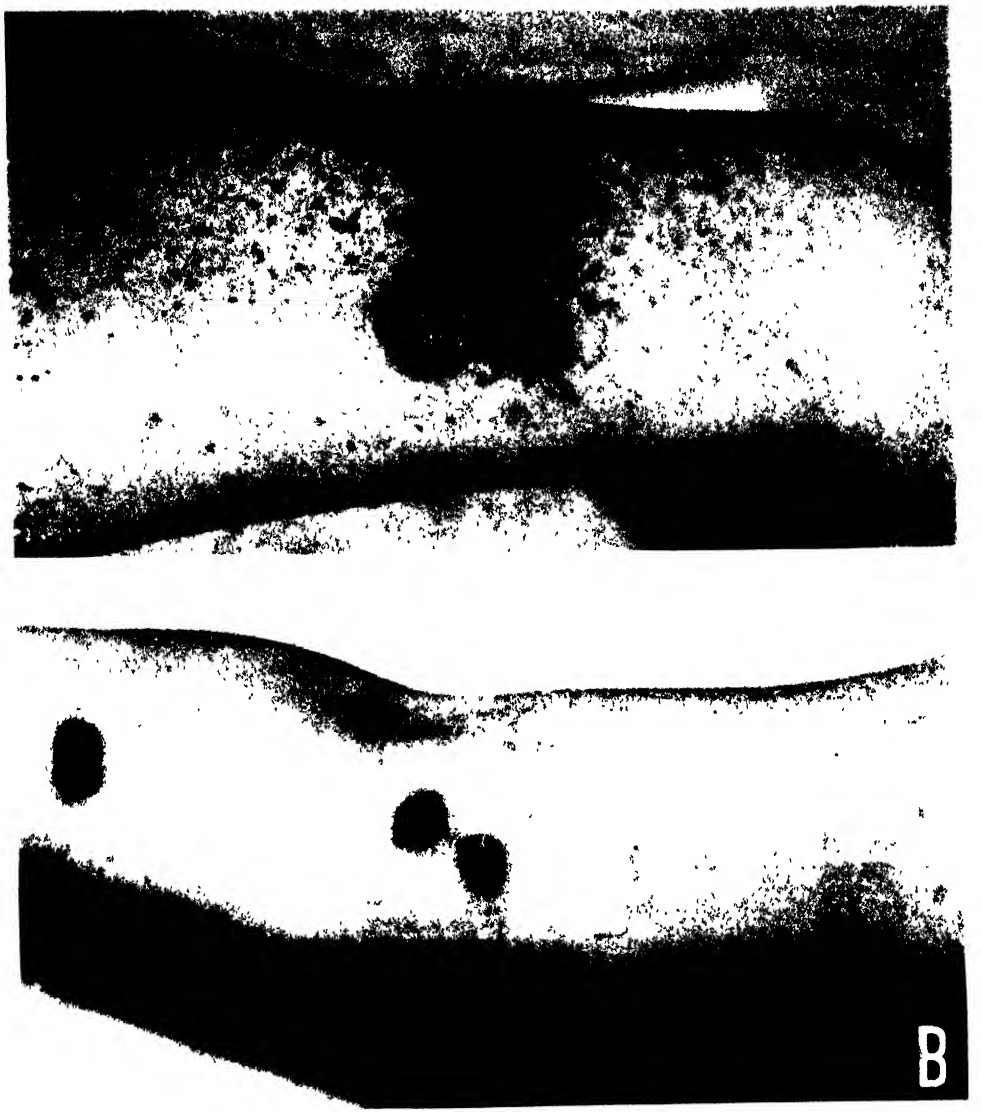

FIG. 60. Sporotrichosis. *A*, the initial lesion, or chancre. *B*, secondary ulcerated lesions extending proximally along the course of the lymphatics.

shaped ulcer with a firm indurated border. In the untreated patient, new lesions may continue to appear indefinitely.

(3) *Disseminated ulcerating type.*—Although similar to the preceding type, this form is distinguished by a tendency to early spontaneous ulceration of the lesions. The ulcerations vary greatly in size and character. At times large crateriform ulcers develop, simulating the lesions of tuberculosis or tertiary syphilis. There is little if any tendency to spontaneous cure. In the untreated patient the general health may become impaired, with the appearance of symptoms of toxemia. Moore and Kile reported an instance of generalized subcutaneous gummous ulcerating sporotrichosis with possible involvement of the lungs. There was a favorable response to treatment. In a case of disseminated cutaneous and visceral infection reported by Collins, death occurred two months after onset.

(4) *Epidermal type.*—The primary lesion in sporotrichosis is nearly always subcutaneous. In some instances the epidermis at adjacent or remote sites becomes secondarily infected, with development of papules, pustules and small ulcers. Rare cases have been described in which the disease is limited to the skin, and in such instances tuberculosis is differentiated with difficulty. The mucous membranes may also become secondarily infected in cases of the disseminated or ulcerating varieties. The organism is said to be capable of remaining as a saprophyte on mucous surfaces after apparent cure, rendering the patient a possible carrier.

(5) *Verrucous dermatitis.*—Perhaps a variant of the preceding type has been described by Smith and Garrett. There was considerable resemblance in their case to blastomycosis with outlying satellite pustules. No lymphangitis developed.

(6) *Systemic type.*—At times S. schencki invades the deeper tissues and organs. In the majority of instances this occurs in the disseminated varieties of infection when treatment is not promptly instituted. The differential diagnosis must exclude cancer, syphilis, tuberculosis and other infections. The bones or joints may be affected, the tibia being the most common site of involvement. Invasion of the muscles and glandular structures may occur, and a number of instances of pulmonary involvement have been reported. Although a common site of involvement in laboratory animals, the epididymis is rarely affected in human beings. Gastrointestinal or cerebrospinal involvement is said to be extremely uncommon. In a case of meningitis studied by Hyslop, Neal, Kraus and Hillman, repeated attempts to culture spinal fluid were fruitless and iodide therapy was of no avail. The diagnosis rested on the observation of sporelike bodies and mycelium in the centrifugated sediment of spinal fluid. There appears to be some doubt as to the exact diagnosis.

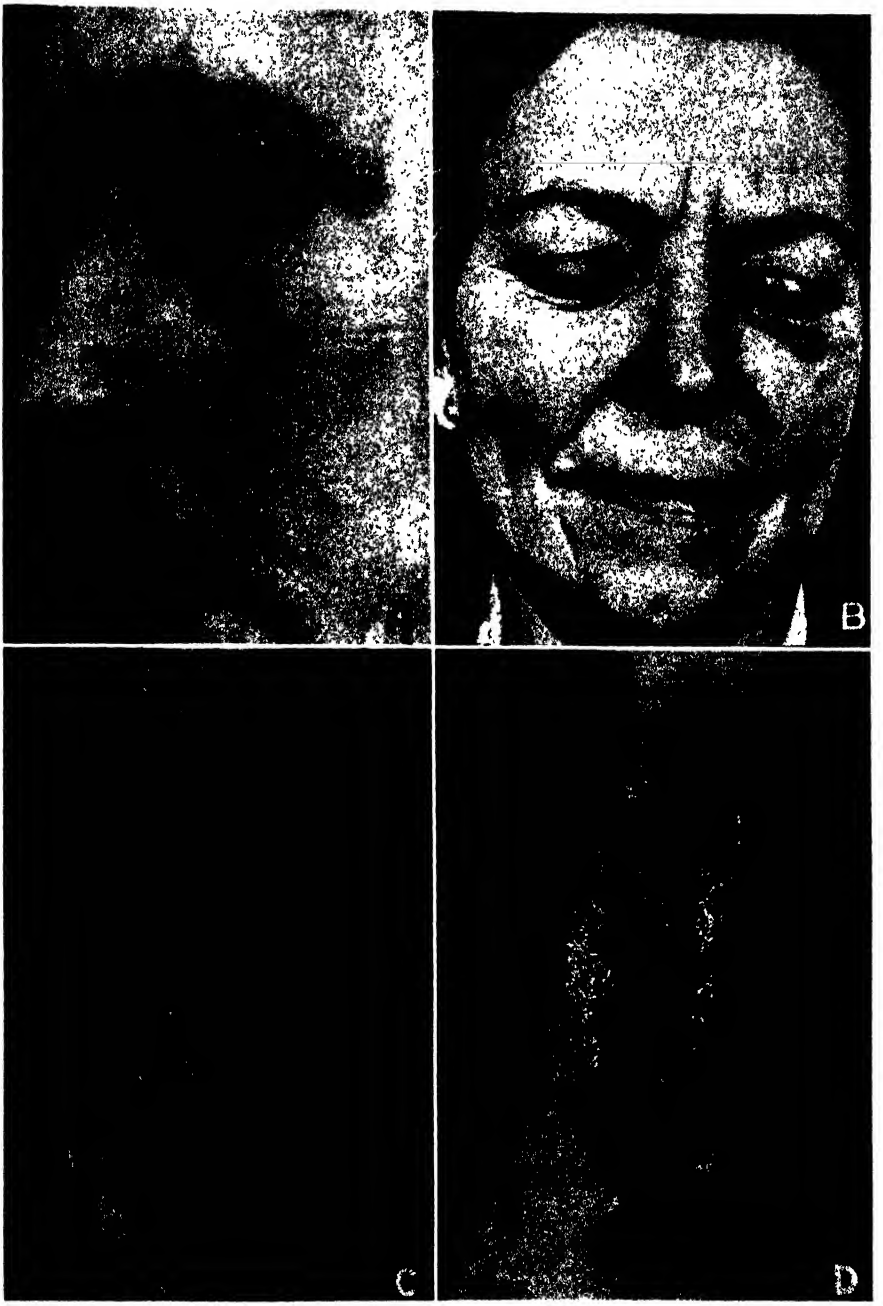

FIG. 61. Sporotrichosis. Four cases of infection involving *A*, the upper eyelid; *B*, the lower eyelid; *C*, the base of the thumb and along the forearm, and *D*, the arm.

(7) *Allergic lesions.*—Sporotrichids, comparable to trichophytids, have been described by de Beurmann.

(d) HISTOLOGY.—D. L. Satenstein's description of a section removed from the edge of an ulcerating lesion is fairly typical of the usual observations:

> The epidermis is irregularly acanthotic. The greater part of the cutis is filled with a dense cellular infiltrate. The blood vessels are markedly dilated, some approaching the size of sinuses. Scattered throughout the cellular infiltrate are many very small blood vessels. The cellular infiltrate is composed of a great many mast cells, some connective tissue cells and a few plasma cells, and in the central portion there is a large group of giant and epithelioid cells. There are also many polymorphonuclear cells scattered throughout the entire zone. There is no degeneration and no abscess formation. The whole process is one of organizing granulomatous tissue with enormous numbers of mast cells. No fungous elements are noted in routine sections, in those stained by Gram's method or in those stained with polychrome methylene blue.

The picture is not in itself diagnostic. One can determine that the process is granulomatous, but syphilis, tuberculosis and other deep mycoses may be difficult to differentiate. It should be remembered that S. schencki is seldom observed in tissue, in contrast to the readily demonstrated presence of most other pathogenic fungi.

(e) IMMUNE REACTIONS.—An agglutination reaction may usually be demonstrated (de Beurmann; Moore and Davis). Du Toit found that serum of patients brought about agglutination in a titer of about 1:600. However, the spores were similarly agglutinated by the serum of normal controls, thus nullifying the value of the test. The complement fixation test is unreliable. According to Bloch, the intracutaneous test with an extract of Sporotrichum is of value; de Beurmann expressed the opinion that a negative reaction rules out the diagnosis of sporotrichosis; there may occasionally be a false positive reaction. Du Toit agrees that a positive skin reaction occurs with regularity in patients with sporotrichosis. In the experimental production of sporotrichosis in a volunteer, the response developed the fifth day following inoculation.

(f) DIFFERENTIAL DIAGNOSIS.—A positive laboratory diagnosis may usually be made without difficulty from cultural studies. The micro-organism is difficult to demonstrate in fresh preparations.

The initial lesion, or sporotrichotic chancre, usually develops on the fingers or hand. When lesions successively appear along the course of a lymphatic chain, the clinical diagnosis may be highly suggestive. Before secondary lesions have developed or if the initial lesion is in an atypical location, the correct diagnosis may not even be considered. The character of the lesions suggests a granuloma, and the differential diagnosis should

exclude another mycotic infection such as coccidioidomycosis, syphilis, tuberculosis, tularemia and pyoderma. The incidence of coccidioidomycosis is highest in California and of sporotrichosis in the Middle West. The evolution of the lesions is usually faster with sporotrichosis than with coccidioidomycosis, and the lesions tend to ulcerate more rapidly. In coccidioidomycosis, secondary lesions usually develop at a remote point. The lesion of actinomycosis or of blastomycosis usually differs greatly from that of sporotrichosis, sinuses draining from deep lesions being present in the former condition and verrucous lesions containing miliary abscesses in the latter. A syphilitic chancre or gumma may be suggested when the initial lesion alone is present. Absence of concomitant symptoms and signs of syphilis may aid, but a cultural diagnosis should here be definitely established, particularly since it can usually be made without difficulty. Tuberculosis develops more slowly, lesions of this character usually occurring in butchers or in patients with foci elsewhere; the pus is usually not so thick or profuse as in sporotrichosis, and the reaction to a high dilution of tuberculin is positive.

Since culture is the only definite method of diagnosis and since it is usually reliable, pus from any suspected lesion should be streaked on agar as described on page 324. If no growth results, agglutination and cutaneous tests may aid in diagnosis. The inoculation of pus into laboratory animals may help. Guinea-pigs are usually immune, but rats are usually susceptible.

The absence of enlargement of lymph nodes and of fever is usually sufficient to rule out tularemia. Pyoderma of granulomatous character is unlikely unless the blood sugar level is elevated.

(g) PROGNOSIS.—Most patients respond well to treatment, even if the disease has escaped diagnosis for several months. In rare instances, when the internal organs become involved, the outlook is more serious and therapy may not prove curative. As with the other deep mycoses, early diagnosis is of paramount importance.

(h) TREATMENT.—(*1*) *Iodides.*—The usual procedure is to administer potassium iodide by mouth three times daily, beginning with 10 drops of the saturated solution. The dose is increased 5 drops daily until the limit of tolerance is reached. The medication should be sustained for several weeks at this point, until long after all signs or symptoms of the disease have disappeared. Sometimes tincture of iodine, Lugol's solution, or colloidal iodine is used, but these forms have no demonstrated superiority except in isolated instances, when they may be better tolerated. The effect of iodides is probably indirect, although Shaffer and Zackheim cured a patient after 13 weeks of therapy with iontophoresis, using a strong solution of iodine, U.S.P. According to Davis, fibroblastic elements are stimulated, and the pro-

liferation of this tissue produces the encapsulation and resultant cure. Some patients are unable to tolerate iodides.

(2) *Roentgen rays.*—It is customary to administer roentgen rays in semi-intensive dosage with some filtration. While there is no direct fungicidal effect, the effect on granulomatous tissue and perhaps the blocking off of the lymphatics are of aid.

(3) *Surgery.*—This is of no avail; but if fluctuation is present, a single incision may be made. It is better still to aspirate the pus without surgical incision.

(4) *Local medication.*—Dressings of Burow's solution (1:15) or of potassium permanganate (1:3,000) may be applied for half an hour several times daily. Gentian violet (1 per cent aqueous solution) may be used to irrigate the lesions, or Lugol's solution (half-strength) may be applied.

(5) *Thymol.*—In case of intolerance to iodine, this may be given a therapeutic trial.

(6) *Penicillin and streptomycin.*—These are ineffectual.

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5. BLASTOMYCOSIS

The North American form of blastomycosis is chiefly seen in the Middle West, particularly in the region around Chicago, but the disease may appear sporadically in any section of the country. There are only three proved instances of the disease originating outside the United States, one each in Canada, England and France. The case reported by Brody occurred in an American soldier who was in France for 10 months before he showed clinical signs of the disease. The presence of budding cells in the diseased tissue was first demonstrated by Gilchrist, in 1896, and the organism causing the disorder was later described in detail by Gilchrist and Stokes. A number of articles and case reports have since appeared, and the nature of the disease is now well known.

(a) PERIOD OF INCUBATION.—Although unknown, it is probably one to two weeks.

(b) ETIOLOGY.—Although Blastomyces dermatitidis is the organism causing American blastomycosis, other organisms are capable of producing lesions which simulate this disorder. The European type of blastomycosis (torulosis) is a distinct entity (Benham). Most of the patients are adults, 50 per cent being over 40 years of age and about the same proportion being between 20 and 40. Most patients are men. The organism may have a saprophytic existence on plants, since numerous Blastomyces are widespread in nature. Two instances of spontaneous blastomycosis in dogs have been reported. Trauma is usually necessary for development of the infection. Scratches, puncture wounds, bruises and the like have been reported as predisposing factors.

(c) CLINICAL CHARACTERISTICS.—The disease may be local or systemic. In most cases the initial lesion appears on the skin. The chief sites are the face, hands, wrists and forearms, although any part of the body may be involved. In some instances the tongue and the lungs are the sites of the first manifestations. On the skin, the first lesion is a papulopustule, which soon becomes crusted. There is peripheral enlargement, and after several weeks a plaque elevated above the surrounding skin is present. Crusting may be of slight amount or may cover the entire lesion. Beneath the crust, the surface shows irregular papilliform elevations and is covered with a

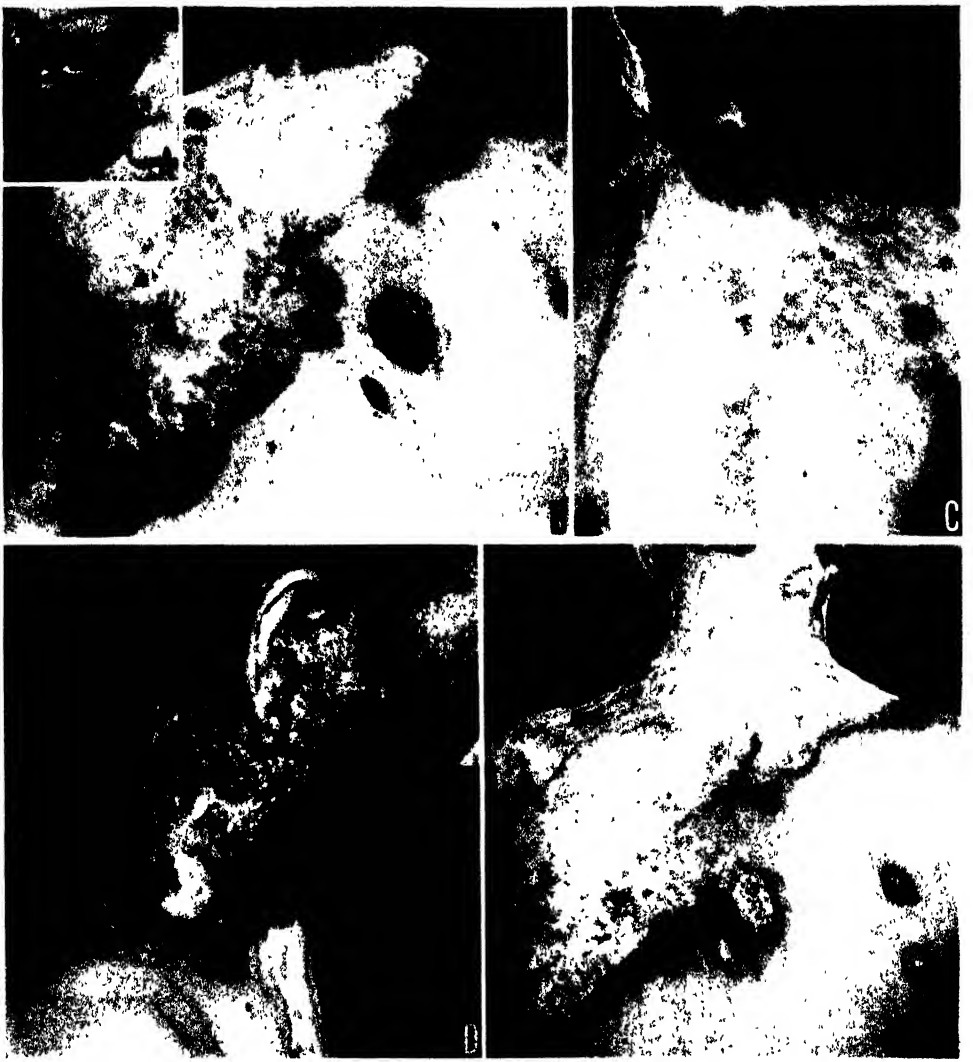

FIG. 62. Blastomycosis: infection of 15 years' duration with widespread involvement of the skin. There was no evidence of internal dissemination of the infection. *A*, *B* and *C*, active verrucous and fungating lesions with extensive scarring after healing. The disease was present on the face, including the eyelids. The scar tissue on the neck prevented free motion of the head. *D* and *E*, marked involution of the lesions six weeks after beginning intensive internal therapy with potassium iodide and roentgen irradiation of the lesions.

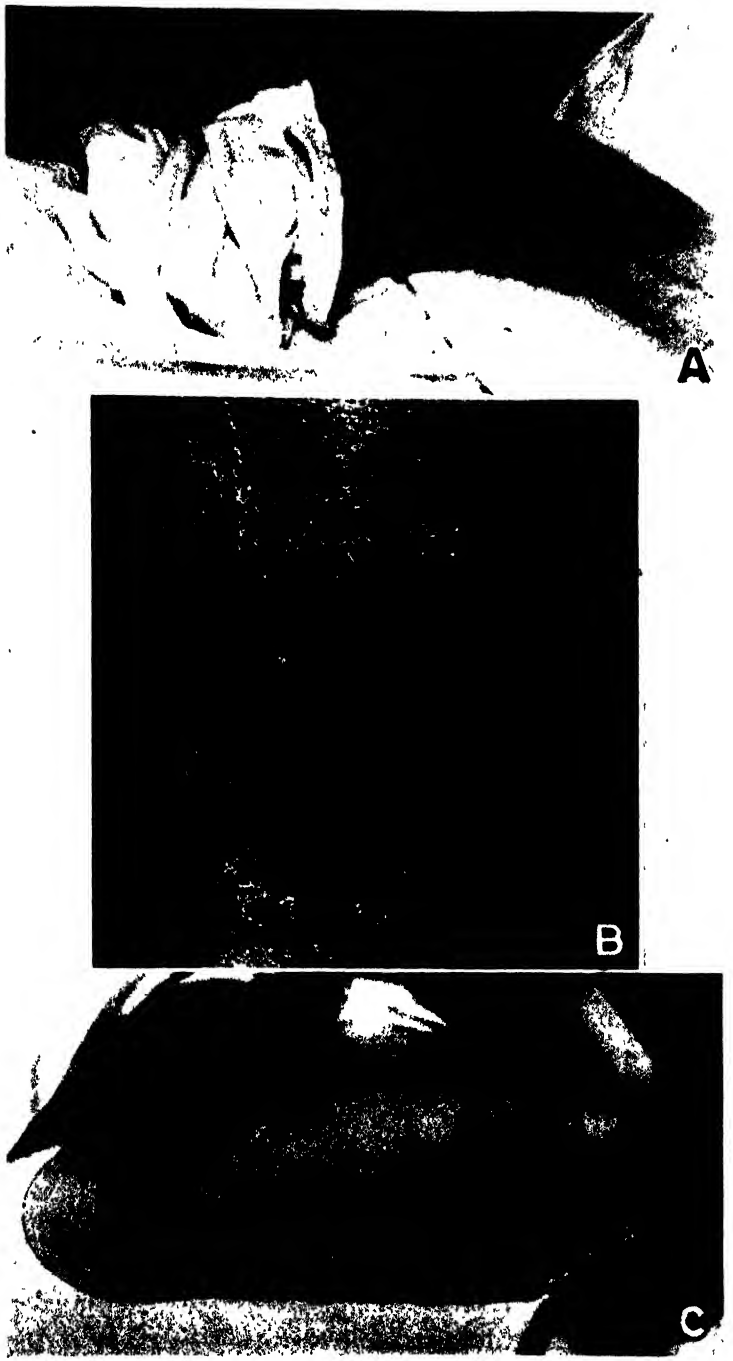

FIG. 63. Blastomycosis secondarily affecting the bones and subcutaneous tissues. The primary focus was the skin. *A*, elbow. *B*, leg. *C*, ankle.

seropurulent secretion, which may be increased by pressure of the affected tissues. According to Ormsby, the border of the patches is one of the most characteristic features. This edge is smooth and slopes down abruptly to normal skin. On its surface are minute abscesses, which may be superficial or deep seated; when the disease is actively spreading they are present in large numbers. The hand lens may be required to see these lesions. Puncture of the minute abscesses along the border of a lesion provides the best material for isolation of the organism. Healing occurs first in the central portions of the lesion and is followed by formation of scar tissue. The patches slowly enlarge, and in half the cases (Ormsby) one or more lesions develop in adjacent or remote parts of the skin.

When systemic dissemination of the organism occurs, any organ or tissue in the body may be attacked. The lungs are the commonest site and often the primary focus; they are affected in over 90 per cent of the cases of systemic involvement. The symptoms at first may be those of an acute infection of the respiratory tract, and a characteristic feature is pain in the chest. Later a syndrome suggestive of tuberculosis is present. The skin may become secondarily infected from deep sites, the organism being carried by the blood stream, in which case subcutaneous abscesses develop. These finally rupture, and one may then note shallow ulcerations, showing granulations at the base, covered with purulent discharge and frequently crusted. When the kidneys become involved, symptoms of nephritis are evident. The bones, particularly the ribs and vertebrae, are frequently affected in the systemic types of the disease, and, according to Stober, the fungus may cause osteomyelitis, periostitis or arthritis. The central nervous system is occasionally involved, and any part of the brain, spinal cord or meninges may become affected. The tongue, the larynx and the intra-abdominal organs have all been reported as occasional sites of the disease but invasion of the intestinal tract is unusual.

(d) HISTOLOGY.—Sometimes the pathologic appearance of a visceral lesion suggests tuberculosis. The presence of central necrosis is characteristic, and the organism is usually associated with leukocytes, red blood cells and débris. Giant cells of the Langhans type may be noted at the periphery. Granulation tissue usually surrounds the nodule. In the skin, marked and irregular acanthosis is a feature. There are also epidermal abscesses, in which budding yeast cells are associated with the type of cells noted in the center of the visceral nodule just described. A cellular infiltrate and interstitial and parenchymatous edema of the underlying cutis are present.

(e) DIFFERENTIAL DIAGNOSIS.—With this, as with other fungous diseases, the causative organism must be demonstrated. Usually this is not difficult

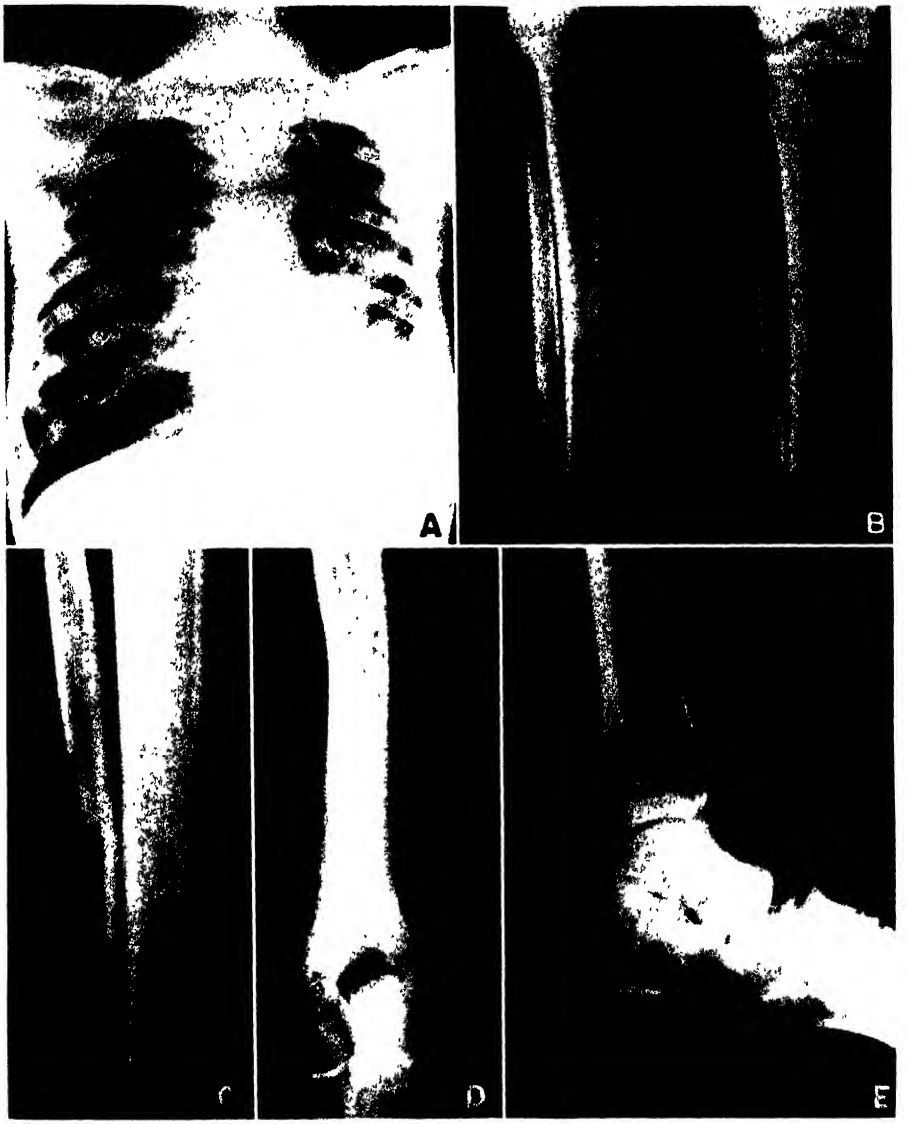

FIG. 64. Blastomycosis affecting the lungs and bones. In *A*, the right side of the diaphragm is in the usual position. The costophrenic angle is clear. On the left, the diaphragm is indistinctly seen; the costophrenic angle appears shallow, and there is evidence of slight pleural thickening. The upper three-fourths of the right lung field shows a definite increased density with multiple interspersed translucent areas. A similar picture is seen in the upper portion of the left lung field. Extending outward from the cardiac shadow in the lower left lung field there is density of a soft character, poorly defined and irregularly mottled. *B*, large saucerized defects of the left fibula with periosteal reaction. Similar destructive defects are seen in the upper shaft of the tibia. *C*, higher magnification of *B*. *D*, left elbow involvement with cortical erosion of the medial epicondyle. *E*, similar destructive changes in the tarsal navicular bone and in the os calcis.

if one examines the small abscesses at the periphery of a cutaneous lesion. Pus is expressed on a clean slide, and a cover slip is dropped on it. Budding cells should be readily observed, but if they are not the preparation may be ringed and left for a few hours, after which budding will probably be noted. The organism is more difficult to isolate from sputum or from secondary ulcers on the skin.

Tuberculosis verrucosa cutis lacks the peripheral miliary abscesses and is usually of firmer texture. Verrucous areas due to the ingestion of bromides develop more quickly and do not show minute abscesses. Prickle cell epithelioma, in contradistinction to the ulcerative variety of blastomycosis, shows a rolled border, more rapid development and usually absence of systemic symptoms; the histology is characteristic. According to Jacobson, the systemic form of blastomycosis resembles granuloma coccidioides so closely that a differential diagnosis is made possible only by laboratory methods, i.e., examination of the organism and inoculation of guinea-pigs. (A guinea-pig is usually not infected with blastomycosis; the animal dies of invasion of C. immitis.) The systemic forms of the disease may simulate tuberculosis. In lung tissue, however, there is less tendency to cavitation (Stober). Osseous involvement is multiple and occurs usually in small bones, with rapid spread and concomitant involvement of the lungs and the skin. Pain is commonly present. A positive reaction to vaccine or a fixation of complement denotes an infection when either is obtained; these reactions are not invariably present in patients with blastomycosis. Smith has pointed out the main features which differentiate true blastomycosis from blastomycosis-like infections. In granuloma paracoccidioides the intestinal tract is commonly affected and the cutaneous lesions are usually in the region of the mouth.

(f) PROGNOSIS.—If the diagnosis is made promptly, before there is dissemination to internal organs, the prognosis is usually favorable. Even after being neglected, the lesions may remain localized and respond to treatment. No one can determine whether or when the disease will become systemic; when this occurs, the outlook is not promising, and, according to Jacobson, 90 per cent of such cases terminate fatally. When the central nervous system becomes invaded, the disease is always fatal.

(g) TREATMENT.—(*1*) *Surgery.*—If the lesion is small and accessible, i.e., cutaneous, surgical excision is probably the surest way of eradicating the disease. Other destructive measures, such as surgical diathermy or actual cautery, may be substituted.

(*2*) *Roentgen rays.*—Lesions not suitable for surgical excision should receive filtered roentgen rays in semi-intensive or intensive dosage.

(*3*) *Iodides.*—Saturated solution of potassium iodide is the usual ve-

hicle. Therapy is begun with 15 drops, well diluted, given three times daily before meals. The dose is increased 5 drops daily until there are symptoms of intolerance. The dosage just below that which produces symptoms should be maintained for several weeks or months, according to the response of the patient. Tincture of iodine is sometimes given for a change. Ethyl iodide by inhalation has also been used.

(*4*) *Specific vaccinotherapy.*—This was advocated by Stober, who has obtained clinical improvement with its use. Martin and his collaborators believe that desensitization should be practiced in all patients found sensitive to the fungus on testing, before any other therapy, such as administration of iodides, is instituted.

(*5*) *Colloidal copper.*—Jacobson recommended intramuscular injections.

(*6*) *Antiserum.*—Martin reported favorably on the use of anti-Blastomyces rabbit serum kept for diagnostic purposes.

(*7*) *Supportive measures.*—They are of vital necessity, particularly in systemic involvement. Rest, sunshine and a nutritious diet may be helpful.

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6. HISTOPLASMOSIS

This is a rare disease essentially affecting the reticuloendothelial cells and when well developed is almost always fatal. This active type is rarely diagnosed ante mortem.

(a) HISTORICAL SURVEY.—The first case of this disorder was described in 1906 by Darling, who was searching for cases of leishmaniasis in the Panama Canal Zone. He considered the causative micro-organism to be a protozoan parasite and named it Histoplasma capsulatum. Rocha-Lima is given credit for first proving the causative micro-organism to be a fungus. DeMonbreun and later Conant as well as others verified this fact and worked out the life cycle of the fungus. Meleney reviewed the subject in a comprehensive monograph. In a later short discussion (1942) he stated that 47 human cases have so far been described.

(b) ETIOLOGY.—The causative micro-organism, H. capsulatum, may be discovered by direct examination or culture of the circulating blood, sputum or feces, by spleen, liver or lymph node puncture, or may be recognized in a biopsy section. According to Meleney, the fungus probably exists saprophytically in nature. Cases have been reported from widely separated geographic sites. No age is exempt and infants and children seem particularly susceptible. A dog and a ferret have been found suffering from the disease. Human subjects with the disease have all come from small towns or farms. The portal of entry may be the lungs, the gastrointestinal tract or an abrasion of the skin (Meleney).

(c) SYMPTOMS.—The classic manifestations are hepatosplenomegaly, septic temperature, anemia, leukopenia and progressive loss of weight. Lymph node enlargement may be the predominant feature affecting these structures in the palpable regions, mesentery, intestines and lungs. The bone marrow may be involved early in the course of the disease. In children the first evidence of the disorder may be related to the gastrointestinal tract with nausea and diarrhea. The other symptoms then gradually appear. In general, the disease runs a more rapid course in children than in adults. The chief lesion may be ulcerative enteritis, as in the case reported by Henderson, Pinkerton and Moore. Pulmonary tuberculosis is frequently found as a concomitant infection. The lungs may be either primarily or secondarily affected and very occasionally are the only site of the disease. When the infection becomes generalized the lungs are almost always involved. Bone lesions and adrenal invasion have been reported. There may be ulcerative lesions of the skin, tongue, nasopharynx or larynx. Purpura has been described, as have papules, plaques, abscesses and patches of dermatitis. Palmer, Amolsch and Shaffer reported an unusual case in which there was mucocutaneous involvement resembling leishmaniasis. Palmer believes that a mild subclinical infection with H. capsulatum is prevalent in certain parts of the country. This explains the finding of pulmonary calcification in patients showing negative reactions to tuberculin and coccidioidin, particularly since many of these patients react to histoplasmin. Christie and

Peterson agreed with this opinion. They found the histoplasmin test positive in 181 children from middle Tennessee who had pulmonary calcification. They cited a possible example of a nonfatal infection with H. capsulatum.

(d) PATHOLOGY.—Gray or white nodules may be noted in the spleen, liver, lungs and intestines as well as other tissues and organs. The mesen-

FIG. 65. Histoplasmosis.

teric lymph nodes are usually involved. The lesions are necrotic, simulating tuberculosis. In the spleen and liver the fungus is found in the fixed reticuloendothelial cells. In other parts of the body it may be found in various phagocytic cells.

(e) DIFFERENTIAL DIAGNOSIS.—In the classic cases, leishmaniasis may be simulated. When lymph node enlargement predominates, Hodgkin's disease, leukemia or lymphosarcoma may be considered. Pulmonary tuberculosis or a chronic ulcer of the skin may be difficult to rule out in other cases. In all instances, the diagnosis is made by demonstration of the causative fungus in smear, culture or biopsy section.

(f) PROGNOSIS.—In the well advanced case the outlook is hopeless, and no therapy has yet been developed which has influenced the fatal outcome.

(g) TREATMENT.—Since the diagnosis is usually made after death or late in the course of the disease, no specific therapy has had a fair trial. Meleney

believes that antimony in the trivalent form (fuadin) and the pentavalent form (neostam) should receive particular attention.

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7. COCCIDIOIDOMYCOSIS

This appears as an acute infection or in the form of granuloma coccidioides. The majority of cases of this disorder originate in the San Joaquin Valley and Los Angeles County, California, and for this reason it is familiarly known as the California disease. There have been scattered cases in the Middle and Southwestern States, but in most instances the patients had lived in California. Smith stated that in a number of cases the disease originated near El Paso, Texas; Farness reported five cases of the disease from Arizona and the remarkable fact that 90 per cent of the Indians in the Pima Reservation gave positive reactions to the coccidioidin test. Reports from other sections make it apparent that the organism may be more widely distributed than is ordinarily thought. Credit for the first description of the condition is usually given to Rixford, who reported his findings in 1894. Cases of a disease with similar features reported from South America are instances of a different disease (granuloma paracoccidioides).

(a) PERIOD OF INCUBATION.—This is between one and two weeks. In an instance of laboratory infection reported by Dickson the period of incubation was seven days.

(b) ETIOLOGY.—The causal micro-organism is C. immitis. This fungus has been isolated from soil, from vegetation and from the internal organs of slaughtered cattle and sheep. Ashburn and Enmons found fungi in 25

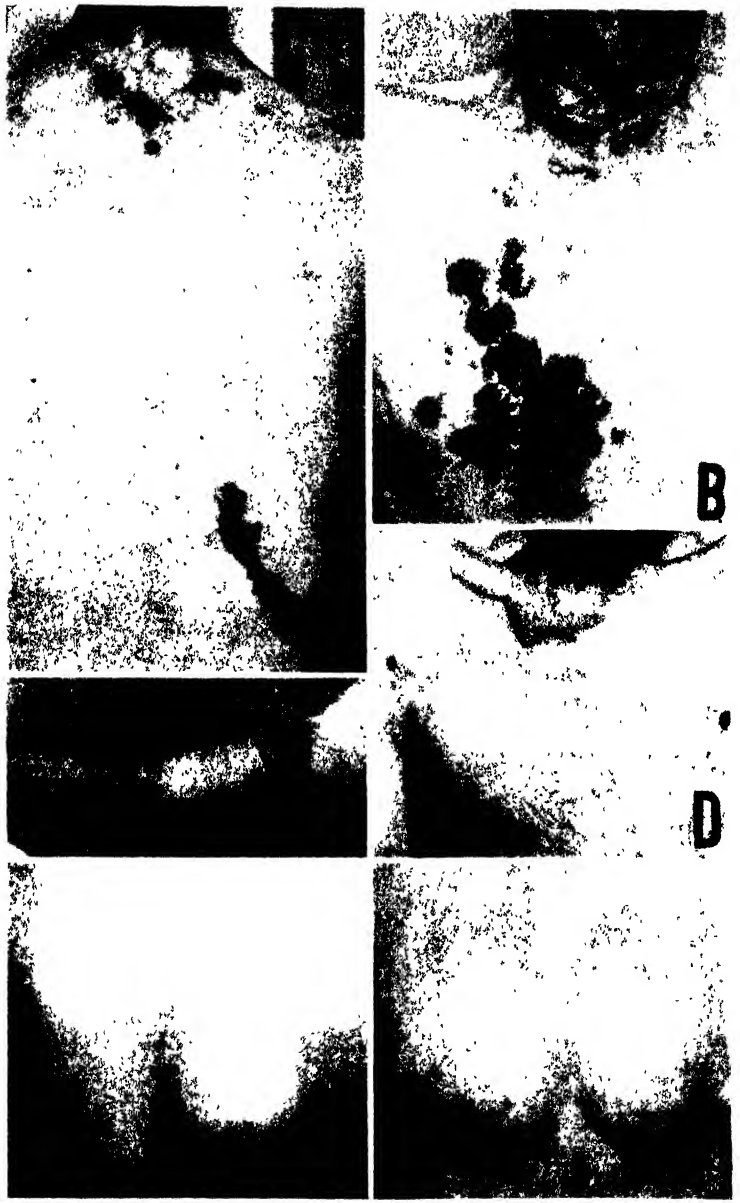

FIG. 66. Coccidioidomycosis, showing different types of granuloma coccidioides. *A*, cutaneous lesions on the back of the neck; the nephrectomy wound was secondarily infected with C. immitis. *B*, verrucous type of cutaneous lesions; note the similarity to blastomycosis. *C*, cutaneous lesions of a patient who acquired the disease in Texas. *D*, abscess resembling a gumma at the sternoclavicular junction. There was a similar lesion on the forehead. *E*, subcutaneous abscess. *F*, two large subcutaneous abscesses. (*A, B, D, E and F were kindly given by Howard Morrow, H. E. Miller and L. R. Taussig, San Francisco; C was supplied by Leslie Smith, El Paso, Texas.*)

of 105 rodents trapped in the desert around San Carlos, Arizona. Definite identification of C. immitis was made in two animals. No instance has been recorded of transmission of the disease from one human being to another. It is thought that most infections occur through inhalation of dust laden with organisms. In a laboratory worker, observed by us, the infection was acquired from the inhalation of spores from an old culture. An injury to the skin may sometimes provide a portal of entry for the fungus. Most of the patients are laboring men, usually engaged in farming, and a high percentage are Mexicans. The epidemiology of acute coccidioidomycosis has been carefully studied by Smith.

(c) CLINICAL CHARACTERISTICS.—The primary lesion may be situated on an exposed part of the skin, but the condition more commonly develops first in the lungs, resulting from inhalation of dust containing the fungus. So-called primary involvement of the pelvis, of the meninges or of the bones is probably the first manifestation of systemic dissemination. The primary invasion of the lungs may be accompanied by a febrile state simulating influenza or bronchopneumonia. According to Dickson most of these patients recover completely. In a scientific exhibit at the annual meeting of the American Medical Association in 1938 he showed roentgen views of chests in which the process had resolved, in patients whose sputum contained the fungus. The roentgenogram of the chest reveals dense shadows in the hilar regions and scattered densities throughout the lungs, indicating parenchymatous involvement. The pulmonary involvement may occur without much fever and with only slight cough. Headaches and backache may occur and blood-tinged sputum may be noted. Pleuritic involvement may cause pain to be a prominent symptom. In cases in which the course is unfavorable, evidences of a spreading infection such as loss of weight, night sweats and fever are observed, and signs of lesions in other locations become evident. The acute infection has been reported only from the San Joaquin Valley, where it is known as valley fever or desert fever. A person of any age and either sex may be affected. In 354 instances of the acute illness, there was only a single death, from coccidioidal meningitis (Dickson). Commonly, from eight to 15 days after the onset nodules of erythema nodosum develop on the shins or in other areas, disappearing spontaneously in four or five days. Recovery from the acute infection usually occurs in three to six weeks.

The manifestations of Coccidioides are various, and the course of the disease is unpredictable. Thus the patient with a systemic infection may succumb within a few weeks, or a chronic focus may remain localized for years.

The primary cutaneous lesions develop as granulomas, which eventually

ulcerate. Healing may occur, or papillomatous fungating lesions may result. The secondary lesions may occur in the subcutaneous tissue, causing flaccid abscesses, some of which reach a large size. Lesions resembling gummas and other granulomas, such as tuberculosis verrucosa cutis, are not unknown. Scrofuloderma may be simulated in the rare eventuality that the disease invades the superficial lymph nodes. The pus present in active lesions is

FIG. 67. Coccidioidomycosis.

thick, yellowish gray and ropy. Temporary healing results from formation of scar tissue. Disfigurement and limitation of movement may be produced.

When generalization occurs, almost any tissue or organ may become involved. The symptoms may be mild at first, and the course may be prolonged. However, if there is rapid and widespread dissemination, a spiking fever, pain, loss of weight and general debility occurs, leading to death within a few weeks. The bones and joints are rather vulnerable, the infection reaching them through the blood stream. The ankle, the wrist and the elbow joints are involved in this order of frequency. An infected joint is swollen and painful and is in effect the site of acute arthritis. The bones of the foot, the ankle joints, the ribs and the vertebral column are those most commonly affected. The lesions are usually of the type of destructive osteomyelitis and are accompanied by slight pain and tenderness. Pus may bur-

row to the surface of the skin, and fistulas may form. When the central nervous system is invaded, evidence of meningitis is usually present. The various internal organs, such as the liver, the kidneys, the spleen and the heart, may all be invaded by C. immitis with widespread involvement. The intestines have never shown lesions of Coccidioides (Ophuls).

(d) HISTOLOGY.—Biopsy material for diagnosis may be either a section of skin or an accessible lymph node. The histologic findings are similar in both tissues. An early lesion, before liquefaction, shows an intense cellular reaction surrounding the organism. The infiltrate contains lymphocytes and epithelioid cells, and one or more giant cells are usually present; often a giant cell contains a parasite. The subsequent picture varies considerably with the type of lesion and the duration of the disease. Frequently polymorphonuclear cells invade the area, and the nodule, which becomes an abscess, is destroyed by progressive suppuration. A wall of plasma cells, lymphocytes and connective tissue separates the pus from the deeper layers. The micro-organism can usually be demonstrated; endospores are nearly always present and because of them it can hardly be confused with any other fungus. The formation of new blood vessels and of fibrous tissue eventually occurs.

(e) IMMUNE REACTIONS.—The reaction to coccidioidin is considered to be specific, denoting infection with C. immitis. One should employ needles and syringes which have not been used for similar tests with other antigens. Since the reaction may remain long after an infection has apparently disappeared, the test is not necessarily diagnostic of a given infective process. As with similar allergic reactions, the interpretation must be correlated with the clinical and laboratory findings. Using an antigen supplied by Dickson, we studied the intracutaneous test in New York. In 400 patients with no evidence of coccidioidomycosis a negative reaction was invariable.

The presence of agglutinins, precipitins or complement-fixing bodies in the blood of infected persons has not been entirely established. Cooke noted positive precipitation reactions, and Cooke and Davis obtained a positive complement fixation reaction. Dilutions of mycelial suspensions were very low, i.e., relatively large amounts of suspension were required.

(f) DIFFERENTIAL DIAGNOSIS.—Demonstration of the organism in pus removed from a lesion in the skin, from sputum, from the spinal fluid or from other sites is usually readily accomplished, and cultures are grown with equal facility. Contamination may complicate the technic. When some difficulty is encountered, animal inoculation may prove of value. The disease should be particularly suspected in a man presenting a granulomatous lesion (usually soft) who has lived or is living in California. The differentiation from tuberculosis on clinical grounds may be difficult. The

cutaneous lesions of coccidioidomycosis have a greater tendency to multiply and their evolution is generally faster. In the lungs, coccidioidal involvement is more rapid and shows less tendency to cavitation. Extrapulmonary lesions, particularly those in bones, are more common than with tuberculosis. The roentgenogram should not be relied on to establish the diagnosis. An early cutaneous lesion of blastomycosis is not likely to be confused with a lesion of coccidioidomycosis, but when the process becomes extensive, particularly when involvement of the internal organs occurs, clinical differentiation of the two mycotic disorders may be impossible without cultural and histologic studies. Syphilis may simulate the fungous disease, but syphilitic gummas are rarely multiple, the serologic reaction may be positive and constitutional symptoms are rarely present. Pyogenic infections, particularly of bone (osteomyelitis), are usually more rapid in their development and more likely to attack children, and lesions of the skin or of other regions are absent. When coccidioidomycosis simulates influenza there is roentgen evidence of involvement of the parenchyma, and the micro-organism (C. immitis) may be demonstrated in the sputum.

(g) PROGNOSIS.—While some cases terminate fatally, it is established that many primary infections clear spontaneously. In the cases of acute involvement of the lungs described by Dickson recovery was invariable. Periods of remission may occur, and relapse after four or more years is not unknown. The mortality is higher among those newly arrived in the endemic territory. It has been said that when patients have cutaneous lesions on the face the outlook is hopeless.

(h) TREATMENT.—In evaluating the benefit from any form of therapy we are handicapped by the fact that the disease shows periods of spontaneous remission. In the cases of acute benign involvement of the lungs, symptomatic measures suffice. The patient should be kept in bed until there is complete recovery. In all instances general supportive and symptomatic treatment should receive consideration. The cases of cutaneous and systemic involvement, particularly of the acute fulminating type, represent a difficult and at times hopeless problem. Radical surgical procedures have been advised for a nidus of infection which is early and localized. Before such a measure is undertaken, a deep focus in the lungs should be excluded by roentgen studies. There are scattered reports of success with the use of various modalities and drugs. A short discussion of these follows.

(*1*) *Roentgen therapy.*—This is useful in causing absorption of the exudate in any granulomatous process, and in coccidioidomycosis, healing of the local lesion is frequently obtained. The effect may be only temporary. Relief of pain may also result from the use of this modality. Intensive or semi-intensive dosage should be used.

(2) *Iodide therapy.*—This usually appears to be ineffective. Some of the reports of improvement were probably due to an erroneous diagnosis (blastomycosis).

(3) *Injection of colloidal copper.*—Although it has been advocated, this treatment is not in common use. The dose is 5 cc. administered intramuscularly every four to seven days.

(4) *Specific vaccinotherapy.*—This has also been reported to be effective. Anderson stated that Jacobson of Los Angeles achieved good results in apparently hopeless cases, corroborating his earlier claims of success.

(5) *Gentian violet.*—This may be used locally in a 1 per cent aqueous solution and intravenously in a 0.25 per cent solution, the total dose consisting of 5 mg. of the dye per kilogram of body weight (Pulford and Larson). If this is exceeded, toxic symptoms may develop.

(6) *Antimony and potassium tartrate.*—The dose is from 2 to 8 cc. of a 1 per cent solution given intravenously. Guy and Jacob, and Tomlinson and Bancroft used this drug in combination with roentgen rays, reporting good results in three patients.

(7) *Thymol.*—The effect of this drug has been investigated by Cox and Dickson. In the experimental animal it was found to be superior to all other drugs which they tested, and a clinical trial in a patient was followed by apparent cure. A 33.3 per cent solution in olive oil was applied locally, and doses of 1 to 6 Gm. daily, dissolved in olive oil and placed in capsules, were taken with meals.

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8. GRANULOMA PARACOCCIDIOIDES

(de Almeida's Disease; Lutz's Disease)

Both de Almeida and Weidman have called attention to the clinical and etiologic differences between this disease and granuloma coccidioides. There are also marked points of similarity, so that only thorough clinical and mycologic study of the patient may reveal the diagnosis. Conant and Howell's observations stressed a close relationship between this disease and American blastomycosis. Their report was discussed by Moore, Weidman and Hopkins, all of whom disagreed with their findings.

(a) Etiology.—The infecting micro-organism is known as Paracoccidioides brasiliensis. The disease is seen only in South America. De Almeida collected 257 cases previously reported as instances of granuloma coccidioides; in all but two the causal organism was probably P. brasiliensis. According to de Almeida, young adult males are chiefly affected, particularly manual workers in agricultural occupations.

(b) Symptoms.—The clinical course is similar to that of granuloma coccidioides except that the portal of entry is usually in or around the mouth. The lesions are granulomatous and may or may not ulcerate; they are usually painful. Secondary lesions may appear in the gums, tongue and face, particularly around the nose. Adenopathy severe enough to simulate that of Hodgkin's disease may be found; in this respect the condition differs from the North American disease. A lymphangitic form is described, beginning in lymph nodes. At times abdominal pain points to involvement of the intestines, a site not known for granuloma coccidioides and blastomycosis. The liver, spleen, lungs and other organs may also be invaded.

(c) Differential diagnosis.—The geographic origin of the patient may assist. The majority (if not all) of patients with infections due to P. brasiliensis are from South America. At times blastomycosis and granuloma coccidioides may be differentiated only by mycologic study although the mucocutaneous involvement is usually distinctive.

(d) Prognosis.—The outlook is almost uniformly hopeless. The patients succumb to the infection within a few weeks to a few months.

(e) Treatment.—Therapy is similar to that noted for granuloma coccidioides. The iodides are occasionally helpful.

FIG. 68. Paracoccidioides (South American blastomycosis). *A*, lymphatic form with swollen lymph nodes and one cutaneous plaque. *B*, pulmonary lesions. *C*, generalized eruption. Lesions are typically present in the region of the mouth. (*Courtesy of Floriano de Almeida and Aguiar Pupo, São Paulo, Brazil.*)

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9. TORULOSIS (EUROPEAN BLASTOMYCOSIS)

This disease is due to a yeastlike organism with a predilection to involvement of the central nervous system. In a recent monograph, Cox and Tolhurst stated that more than 100 cases have been reported. In 1895 Busse and Buschke described cutaneous lesions due to yeastlike organisms. In 1905 von Hansemann reported the first recognized case of infection of the brain. In 1916 Stoddard and Cutler first described the clinical and pathogenic characteristics of the disease, the cultural findings and results of animal inoculation of the causal organism. Torulosis has been reported from most parts of the world; in the United States the majority of cases occur along the eastern seaboard or in the South. It is not uncommon in South Australia.

(a) ETIOLOGY.—The micro-organism, Cryptococcus hominis (Torula histolytica), is commonly found as a saprophyte on the skin and also in the throat and the gastrointestinal tract. It is to be found on many plants. It is probable that some strains assume virulence. As a rule the exact portal of entry is obscure, although it is thought that the upper part of the respiratory tract is the usual route. Men are affected twice as frequently as women. Two thirds of the patients are between 30 and 60 years old (Levin). In over 250 specimens of spinal fluid from patients with syphilis, furnished us by Girsch Astrachan and by Bruce Webster, we found no evidence of infection.

(b) SYMPTOMS.—The symptoms are usually referable to the central nervous system. As a rule, the disease begins insidiously. A subacute upper respiratory tract infection may be the first evidence of invasion. Persistent severe headache, stiffness of the neck and vomiting are characteristic. Later, dimness of vision or actual blindness may occur. Paralysis and convulsions are not uncommon. The patient may be afebrile or may have intermittent low grade fever. Stiffness of the neck, neuroretinitis, choked disks, diplopia, nystagmus, strabismus and hyporeflexia may be found. Laboratory investi-

gation is usually of no help until the spinal fluid is examined. This is usually under increased pressure and contains an increased number of cells, mainly lymphocytes. An increase in the amount of albumin and of globulin and a meningitic colloidal gold curve are sometimes observed; the chlorides may be diminished. There is a progressive loss of weight; after several weeks, months or even years the patient becomes comatose and dies of respiratory failure.

Cutaneous lesions, alone or associated with the lesions in the central nervous system, are noted in approximately 5 per cent of patients. These consist of localized abscesses and tumefactions; later, ulcers may form. Enlargement of lymph nodes is present in about 15 per cent of infections and Hodgkin's disease has been confused in at least one case (Wile).

According to Weidman, the usual cutaneous lesion is a granuloma, which develops so rapidly that abscess formation is simulated. There is usually no surrounding erythema or pain. The lesion may regress spontaneously in four to eight weeks. In all instances the cutaneous variety later assumes the cerebrospinal form. Wile noted subcutaneous and deep-seated nodules resembling ecchymoses, ranging from a small plaque to involvement the size of a hand and having no tendency to ulceration.

Generalization with particular involvement of the lungs is a rare possibility. In the case reported by Fitchett and Weidman, there was widespread visceral involvement and Hodgkin's disease was also present. It is uncommon for the disease to affect the mucous membranes, the bones or the joints.

(c) DIFFERENTIAL DIAGNOSIS.—Tumors of the brain, tuberculous meningitis, syphilis and other disorders affecting the central nervous system may be ruled out by the symptoms, by the physical findings and by culturing spinal fluid on dextrose agar. The last-mentioned procedure may be the only possible means of definitely deciding the diagnosis. Torulosis should be considered whenever symptoms are referable to the central nervous system. The diagnosis is rarely made before death.

(d) PATHOLOGY.—Various sites of the central nervous system may be involved, and the findings are various. Cysts and gelatinous tumors are common. The inflammatory reaction is usually slight, but endothelial hyperplasia is marked, and giant cells are usually noted. Caseation is sometimes seen, and in the case of Cudmore and Lisa there was a cicatrix in the brain. The organism may usually be seen in large numbers.

In cutaneous torulosis a granulomatous process is present, with enormous numbers of giant cells of the foreign body type, very little inflammatory reaction and a peculiar form of caseation which may lead to ulceration.

(e) DIAGNOSIS.—This is established by demonstrating by the India ink technic, or by culture, the thick-walled budding cells in centrifuged specimens of spinal fluid, sputum, blood or urine (see pp. 336 ff.).

(f) PROGNOSIS.—When the disease affects the central nervous system the outcome is invariably fatal. This may be partly because in most cases the diagnosis is not made until after death and suitable treatment has not been instituted.

(g) TREATMENT.—Symptomatic measures are indicated; these include sedation and repeated withdrawal of spinal fluid. Fever therapy may be considered, although we have had no experience. Treatment with the sulfonamide drugs has been advocated and there are several favorable reports. It is advisable to administer both sulfadiazine and penicillin in large dosage and, if improvement is noted, to continue both drugs for several weeks after all symptoms have disappeared. The administration of iodides to the point of intolerance may also be considered.

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10. RHINOSPORIDIOSIS

This mycosis is uncommon in the United States, the majority of cases being reported from India and Ceylon, with only a few cases from widely scattered parts of the world.

(a) ETIOLOGY.—Almost all humans affected are children and young men. Horses, cattle and mules have been found infected. Trauma has been considered a factor. There is no evidence that the fungus causing the disease (Rhinosporidium seeberi) is air-borne. Stagnant water is suspected as a source.

(b) CLINICAL CHARACTERISTICS.—In a predominant number of cases, the disease is confined to the anterior nares. Occasionally it spreads to other sites on the face or to the posterior nares. At first there is a mucoid discharge and pruritus is troublesome. The lesions develop slowly, are sessile but later tend to become pedunculated and may eventually weigh up to 20 Gm. The tumor mass is red, soft, moist, friable and lobulated. Older lesions become verrucous and may resemble a cauliflower. When the disorder is neglected, the pharynx and larynx are not uncommon sites for extension, and obstruction is produced. The conjunctiva may be involved; the lesions are red, polypoid and speckled, and bleed readily.

(c) HISTOLOGY.—There is downgrowth of the epithelium, which is somewhat acanthotic. The connective tissue proliferates, and new blood vessels are present in large numbers. Chronic granulation tissue is present in the cutis. The predominant inflammatory cell is the plasma cell. Fungi surrounded by leukocytes may be present in clumps in the upper cutis, detectable clinically as white or yellow specks.

(d) DIFFERENTIAL DIAGNOSIS.—The site of the lesion, the readiness to hemorrhage and the mottled appearance of the lesion are suggestive points, and a definite diagnosis can usually be established by direct examination of material from the lesion or from the nasal secretion. The lesions of blastomycosis and of paracoccidioidal granuloma are not vascular but are firm, papillomatous and crusted. Tuberculosis affecting the anterior nares would be present only if the patient had pulmonary involvement. Carcinoma is rarely seen in this site and usually shows a rolled edge. Granuloma pyogenicum bleeds easily but is a firmer, more rapidly growing tumor.

(e) PROGNOSIS.—The lesions are usually only of local significance. Unless thoroughly destroyed, they tend to recur.

(f) TREATMENT.—Some form of local destructive treatment, such as electrodesiccation, is indicated.

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11. ASPERGILLOSIS

This is an uncommon and ill defined disorder which usually affects the lungs. It is due to one or more species of Aspergillus.

(a) ETIOLOGY.—In our routine work we commonly isolate by accident one of many species of Aspergillus. The assumption is that this genus is widespread in nature. Thom and Church were able to collect 350 different species. Aspergillus fumigatus has been isolated more frequently from diseased tissue than any other species, and the consensus is that it may be pathogenic (see Chapter XXXIV, "Fungi Probably Pathogenic"). Pigeons, parrots and other birds are vulnerable and may be the medium of exposure. Bird fanciers, grain handlers and wheat threshers are said to be prone to the infection. In a group of cases reported by Sayers and Meriwether, A. fumigatus and Aspergillus niger were thought to be the cause of a lung infection simulating miliary tuberculosis.

(b) SYMPTOMS.—The lungs may become primarily involved. The course may be acute or chronic. Acute bronchopneumonia is simulated in the first instance and tuberculosis in the second. According to Jacobson, hemoptysis is commonly associated with this infection. There is less emaciation than with pulmonary tuberculosis of similar involvement. The recovery of a species of Aspergillus from lesions on the skin may at times be significant (see section on otomycosis, pp. 168 f.), but careful controls and experiments are required, since the organism is notoriously a secondary invader.

(c) DIFFERENTIAL DIAGNOSIS.—If the lungs are infected, the chief disease to be differentiated is tuberculosis. Repeated failure to isolate tubercle bacilli, the freedom of the apexes of the lungs as seen by roentgen study, the atypical onset and course and at times the history of exposure all favor the diagnosis of mycotic infection. Infection with M. albicans may be readily differentiated by microscopic and cultural studies. Before making a diagnosis of probable aspergillosis, one must exclude other diseases and must repeatedly isolate the micro-organism in massive quantities. Aspergilli may be cultured from normal sputum.

(d) PROGNOSIS.—The course of the disorder may be prolonged.

(e) TREATMENT.—1. The origin of the infection should be ascertained if possible, and the patient may be advised to change his environment or occupation in order to escape further exposure. A gauze mask should be worn by grain threshers, if susceptible.

2. If tuberculosis can be definitely excluded, potassium iodide should be employed in ascending dosage.

3. Bed rest, wholesome food and fresh air are advisable.

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12. MYCOSES OF THE LUNGS

Of the invasive, deep-seated and potentially fatal mycotic infections, coccidioidomycosis is the only one that is regularly acquired by inhalation. This results in an acute inflammation of the lungs simulating one of the common acute upper respiratory diseases. Most patients recover spontaneously. The lungs may be involved late in the course of the disease in the occasional instance in which there is not complete recovery from the initial acute infection. It is probable that a primary and benign form of histoplasmosis affecting the lung parenchyma is not uncommon in Tennessee and in some other sections of the United States. With spontaneous healing calcification occurs, with the final roentgen appearance of a miliary nodular calcific process. With the other rare invasive fungous infections, the lungs may share in a widespread involvement of many tissues and organs. Infections due to B. dermatitidis, S. schencki or A. bovis may become systemic and the lungs become invaded through the blood stream. Another fungous disease of the lungs, due to inhalation of A. fumigatus, is frequently of occupational origin among grain workers and is usually comparatively banal, with a good prognosis for cure. In general, these infections are not difficult to diagnose provided the possibility of fungous disease is kept in mind. Tuberculosis may be simulated. The latter disease is distinguished by the history, the sputum examination and the appearance of the roentgenogram. In general, tuberculosis has a predilection for the apexes, while the typical sites of involvement of the mycoses are the middle and lower pulmonary fields. Positive identification of the causative fungus is requisite to establishment of diagnosis. This is accomplished by study of a fresh mount (as in actinomycosis), by examination of a specimen mounted in hydroxide (coccidioidomycosis), by culture (sporotrichosis) or by a combination of these methods. Skin tests using specific antigens may be useful, particularly with histoplasmosis of the benign type. It should be remembered that tuberculosis also may be present.

In addition to the aforementioned well defined and well recognized types of involvement of the lungs, there is a considerable number of cases

in which the lung disease is assumed to be caused by fungi, usually without substantial proof. Monilia albicans may be particularly singled out as frequently blamed because it is found in the sputum of patients with an atypical disorder of the lungs. During the past few years we have studied the role of fungi in chest diseases. The results show that M. albicans is a frequent secondary invader of diseased tissue (such as carcinoma) but rarely initiates disease. It was thought to be the primary cause of death in only one instance, a conclusion which could not be substantiated by postmortem examination. In three other cases there was good evidence that M. albicans was the causal invader and cure followed the administration of iodides. Our study included specimens from 250 patients. In over 100 ambulatory patients in a control series with no pulmonary symptoms, there was a high percentage of air-borne fungi in the sputum, but fewer instances in which M. albicans showed so vigorous a growth. From our observations and study we conclude that one must be careful in assigning a pathogenic role to fungi because they are found in sputum. The air-borne molds, with the exception of A. fumigatus, may be dismissed as unlikely pathogens. Monilia albicans may very occasionally be pathogenic. The finding of known pathogens such as A. bovis (in granules) and C. immitis must always be considered significant.

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CHAPTER XI

Fungous Diseases and Compensable Dermatoses

AN ACCURATE (cultural) diagnosis of fungous disease or adequate proof that such a disease is not present may be of special importance to patients who apply for help under one of the state laws on workmen's compensation. If a mycotic disease is contracted while at work, the worker is entitled to compensation. The hands are the usual site of the rash. There is no good evidence that contact dermatitis predisposes to the invasion of fungi. Fungi certainly would not select inflammatory tissue such as an eczematous patch from choice. The dermatophytes prefer noninflammatory tissue. However, we have frequently observed that an acute tinea may be followed by increased susceptibility to sensitizing and irritating agents, expressed as an eczematous eruption, often supervening on and becoming more serious than the original fungous disease.

1. PRIMARY DERMATOPHYTOSIS OF THE HANDS

Sometimes the patient's work may be directly responsible. For instance, the occurrence in a bank teller suggests an occupational origin, since handling of paper money may be the source. A fellow worker who has the disease may be the important focus. The diagnosis of primary dermatophytosis of the hands should not be based solely on clinical grounds but should be verified by microscopic and cultural studies. Each case presents an individual problem, and it is important at least to attempt to trace the origin of the proved infection. In this way additional proof is gained of the occupational or nonoccupational origin of the infection, and prevention of further spread may be obtained. In many instances, taking an accurate history will reveal other cases. While the diagnosis of primary fungous infection of the hands is probably too frequent, the disease should not be overlooked.

2. DERMATOPHYTID SECONDARY TO A FUNGOUS FOCUS

The criteria for the diagnosis of dermatophytid are given in another part of the book. This diagnosis should never be made from clinical inspection alone. There must be a fungous focus elsewhere, a positive reaction to trichophytin and a reasonable certainty of exclusion of all other possible cutaneous disorders, particularly dermatitis venenata.

3. NONMYCOTIC DISEASE

There are numerous types of rash which may appear on the hands. A negative reaction to the intracutaneous trichophytin test will exclude dermatophytid. It is beyond the province of this work to discuss further the differential diagnosis of eczematous eruptions of the hand, such as dermatitis venenata, pompholyx, acrodermatitis and pustular psoriasis (see the section on differential diagnosis of dermatophytosis, Chapter IX, pp. 120 ff.).

4. THE RARE MYCOSES

Such infections as sporotrichosis may be of occupational origin. Pulmonary moniliasis and aspergillosis in grain handlers have been reported.

Lane classified fungous diseases of employees who are examined for industrial disability as follows:

(a) Primary mycotic infection due to poor working conditions or contact with an infected fellow worker.
(b) Exacerbation of a previous mycotic infection due to working conditions.
(c) Fungous infection superimposed on industrial dermatitis.
(d) Industrial dermatitis following fungous infection.
(e) Mycotic infection bearing no relation to occupation.

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PART TWO

LABORATORY METHODS

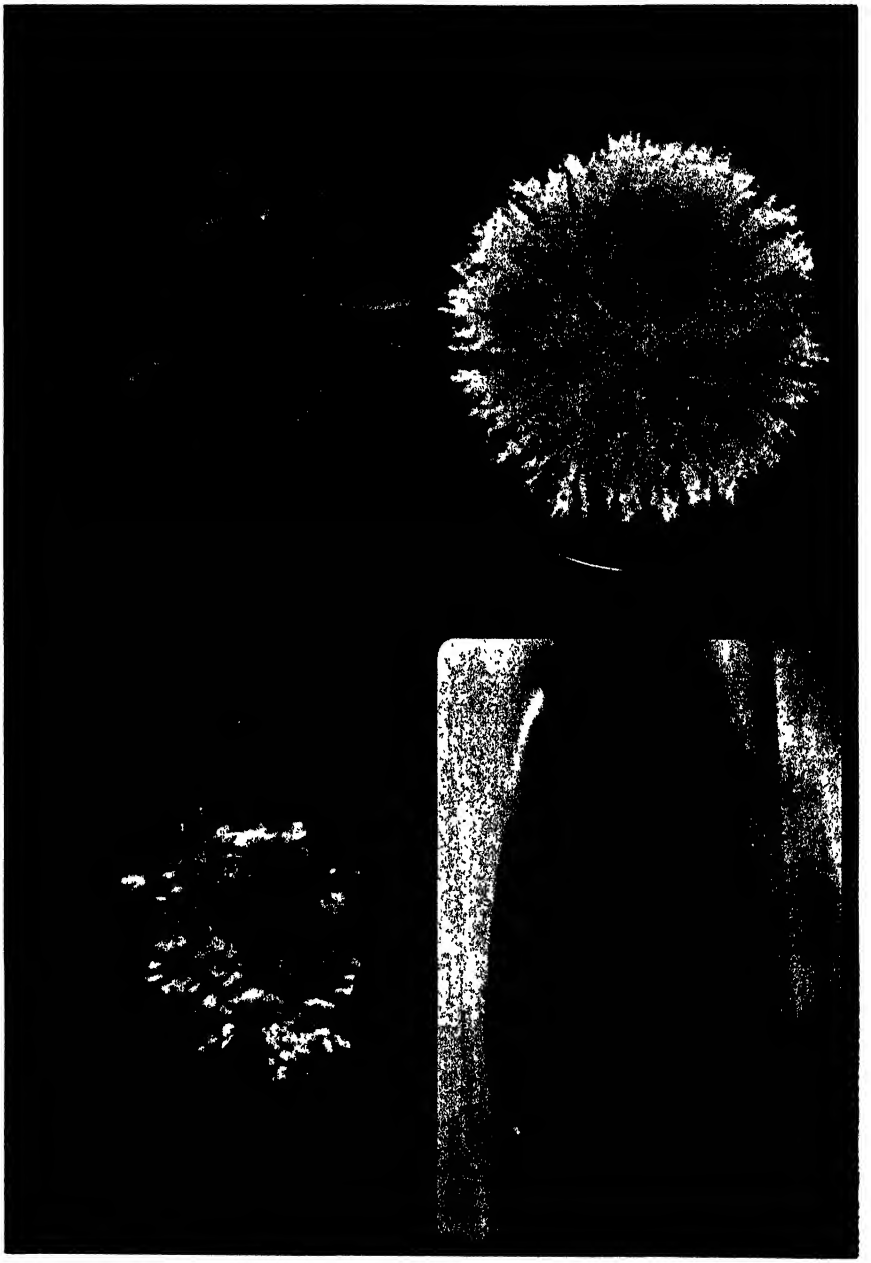

PLATE II. Many fungi show characteristic colors in culture. The color is inherent and not dependent on exogenous factors. *Upper left,* Microsporum ferrugineum; *upper right,* Microsporum fulvum; *lower left,* Achorion schoenleini; *lower right,* Trichophyton violaceum.

CHAPTER XII

Introduction

THE procedures for laboratory investigation of mycotic disorders are, on the whole, not difficult to master. The methods outlined here are those which we use in our mycologic laboratory at the New York Hospital and in private practice. They have been proved by experience to be efficient. We realize that one cannot instruct the novice in all the minute details without practical demonstration. The mediums and technic of the mycologist differ somewhat from those of the bacteriologist. Since most fungi grow well at room temperature, a higher temperature is usually unnecessary. Moreover some fungi which grow luxuriantly at room temperature will scarcely develop when incubated at body heat. This effect may be in part due to desiccation of the agar (lack of moisture) as well as to unsuitable temperature. Culture of bacteria requires incubation in an elevated temperature. For this reason bacterial contamination of fungous cultures is rarely seen; although many species of bacteria normally are present in the mouth, scrapings from the tongue on acid dextrose agar incubated at room temperature are singularly and strikingly free from bacterial contamination. The chief contaminants are other fungi, such as Penicillium or Scopulariopsis. Elaborate mediums are not required, and except in detailed work and investigation of minute points only a few mediums are necessary, unless one is attempting to isolate Actinomyces (closely related to bacteria) or Blastomyces. In the former case, incubation at body heat and the use of blood for enrichment may be requisite. In addition, some strains grow only under anaerobic conditions. Blastomyces dermatitidis usually requires incubation at 37 C., with blood agar for the primary isolation. At other times growth occurs at room temperature.

Another difference between growth of bacteria and growth of fungi on artificial mediums is partly due to the method of incubation. Whereas bacteria multiply and colonization is detectable after a few hours or within a few days, a comparable status with fungi requires from several days to

three or four weeks. On the average, seven to 10 days elapse before a definite report of the species of infecting fungus can be delivered.

The large majority of specimens intended for mycologic examination are derived from the cutaneous surface. These include scales, macerated skin, pieces of nail, the roofs of vesicles, pustules or bullae and hairs. At times the specimen may consist of pus from deep cutaneous lesions (either open or closed) or from an internal source (such as an appendiceal abscess). The material may be one of the body fluids, such as blood (for histoplasmosis?), spinal fluid (for torula?) or bile. The sputum usually contains one or more species of fungi. Due care must be exercised in differentiating between the pathogenic and the saprophytic fungi which will be obtained. Study of the oral mucosa (particularly of the tongue) and of the stool (especially in cases of moniliasis) is frequently an integral part of the mycologic examination. Routine examination of a vaginal discharge is probably a good policy.

Pathologists are frequently called on to make an unequivocal diagnosis from specimens of tissue taken by biopsy or post mortem. There is often a close resemblance between the mycoses of granulomatous nature and tuberculosis and, in the absence of the infecting micro-organism, a definite diagnosis without directive clinical information may be impossible. As in tuberculosis, the fungous disease may be acute, in which abscess formation results, or chronic, with the development of giant cells, often in tubercle-like fashion, together with plasma cells, lymphocytes, epithelioid cells and occasional mast cells.

CHAPTER XIII

Precautions against Laboratory Infections

IT IS important never to leave infected slides or instruments where they may be accidentally handled. When they have been used, it is better to dispose of them immediately or to place them in a 10 per cent solution of cresol. The use of rubber gloves may be advisable in theory, but it is seldom carried out in practice. The use of soap and water at frequent intervals is a wise routine. With most of the dermatophytes there is little danger of inhalation of spores from colonies. For this reason it has not been our policy to wear masks when working with them. When one is working with cultures of C. immitis, danger of inhalation is real and a mask should be worn; moreover, care should be taken that there is no draft, as from an open window or from a fan. Another important consideration has to do with old cultures. When the medium dries, it may be incorrectly assumed that the fungi are dead. Through insufficient sterilization they may still be viable and able to cause infections. The floors, the table tops and other accessible and used parts should be frequently cleaned. Sponging with a 3 per cent solution of cresol followed by the use of soap and water is effective.

The use of a motorized burr to remove nail tissue has become fairly common. We advise against using this device in a laboratory, clinic or office. Sterilization of the instrument is difficult, and it is difficult to keep the infected nail material, which is pulverized by the rapidly revolving burr, from being disseminated through the air. If the instrument is used, a mask should be worn and newspapers on which the dust has been collected should later be burned.

CHAPTER XIV

The Microscope

THE microscope is an important instrument in mycologic work. A beginner should become familiar with the various parts and learn the few necessary details of its proper care. The oil immersion objective is only occasionally necessary, as in the examination of scales from a lesion suspected of being erythrasma. The low power objective is useful in locating the most desirable field for examination. A trained observer may detect fungi by their appearance under low magnification (approximately × 100). For finer details and for confirmation of the original observation, study of the material under the high dry objective (above × 400) is usually profitable. We have found a third objective giving an intermediate magnification (about × 200) useful for the closer examination of many slides. This has a larger field and a greater depth of focus than the ordinary high dry objective; at this power, identification of structure is readily attained. If the preparation is flooded with solvent, some of it is almost certain to run over onto the stage of the microscope. If the slide is then removed and the stage washed with a damp cloth, no harm will result. Unless the solvent is removed, the stage will become tarnished and discolored. If the objective accidentally touches the solvent, the solution should be wiped off promptly with a wet microscope paper; otherwise vision is interfered with. Only soft lens paper, especially made for the purpose, should be used to clean the lenses in the eyepiece and objective. The beginner often makes the mistake of opening the diaphragm too far, allowing an overabundance of light to pass through. Since the material is usually unstained, the light must be subdued in order that fungous elements may be visible.

CHAPTER XV

Collection of Diseased Tissue

SELECTION of suitable material for direct examination and culture is most desirable if one is to elicit information of value. There are several rules of procedure, but one cannot always give directions for the individual case. Here, as in most technical fields, experience is valuable.

If possible, tissue should be removed from a lesion of recent origin. Since treatment may affect the abundance and the stage of development of the fungus, untreated areas are preferable. The components in the medicament may obscure the fungus or confuse the observer by their similarity to fungi; i.e., oil droplets may look like yeast cells. When secondary infection due to pus-forming bacteria has obscured the primary fungous infection, mild bactericidal therapy for a few days will usually enhance the probability of recovering the fungus.

Removal of incidental saprophytic fungi from the broken surface of the lesion may usually be accomplished by cleaning with 70 per cent ethyl alcohol.

If there are many types of lesion, specimens from all should be secured. An abundance of material is usually desirable, but a small quantity of good material is better than a large amount of unselected tissue.

With ringworm of the scalp the infected hairs should be selected while the patient is observed under filtered ultraviolet rays. Samples of many hairs may be obtained by scraping across the infected patch with a sharp scalpel. The first scrapings are used for direct examinations. Further scrapings from this cleared surface are transferred directly to the culture medium by cutting into its substance with the scalpel. Filtered ultraviolet rays reveal the sites of tinea versicolor, which may not be readily discerned in daylight.

When infection results in a porous condition of the nail, the deeper part of the invaded tissue is most apt to contain the pathogenic fungus in pure form. The affected portion of the nail should be cut away; this is advan-

tageous not only for obtaining a satisfactory specimen from the exposed base but is also important in therapy (see under treatment of onychomycosis, pp. 135 ff.). For direct examination, a small portion of material from the nail bed is more desirable than large clippings or even the entire nail. When there is little horny (scaly) material, it is impracticable to attempt to identify the fungus by direct examination. In this case one must rely on cultural methods. With the lesions under treatment, the amount of material to be obtained may be reduced, and cultural methods alone will be effective in demonstrating the continued presence of a pathogen. It may be mentioned here that fungi are frequently to be found at the sites of apparently cured lesions; in such a case, unless treatment is continued, the infection may recur.

If mycosis of the lungs is suspected, a specimen of sputum or a fragment of tissue should be obtained bronchoscopically. Thus one may determine whether Monilias, Actinomycetes or other organisms noted in a direct smear or in culture from a casual specimen of sputum are actually invading the lung or are merely present in the mouth as saprophytes. If the fungous material is found in large amounts or if the same species of micro-organism is repeatedly isolated in the presence of negative results of studies for tuberculosis, carcinoma and other pulmonary diseases, primary fungous disease may be considered probable.

While it is often customary to collect a pathologic specimen from a patient and place it on a sterile slide or in a sterile container for inoculation of mediums and examination at a later time, we prefer to transfer material directly from the patient to the culture medium. This makes possible the selection of tissue most favorable for culture and also cuts down the incidence of contaminants.

CHAPTER XVI

Care of Instruments

THE following instruments are placed on our tray to be used in obtaining specimens:

1. Bard-Parker scalpels (curved blade)
2. Heavy duty cuticle clipper, to remove infected nail tissue
3. Scissors (sharp, pointed, curved)
4. Forceps
5. Syringe (tuberculin) with 20 gage needle, to aspirate pus
6. Safety razor of standard make, to shave scalps when indicated

If sterilization is effected by boiling, the cutting edges of the instruments soon become dulled. In order that this may be prevented, the instruments after use are immersed in a 10 per cent solution of cresol for at least half an hour. They are then washed in water and placed in a 70 per cent concentration of alcohol (saturated with sodium bicarbonate), where they are left until used. There is no rusting in either solution, and the instruments can be left in either for an indefinite period. The syringe and the needle are sterilized by placing in boiling water for 10 minutes.

It is well to have from four to six scalpels available so that examination of patients will not be retarded because of the time necessary for sterilization. The sharpest blade, which may be identified by placing a piece of adhesive plaster on the handle, should be used when working on nails.

CHAPTER XVII

Care of Glassware

USED slides are first separated from the cover slips; both are then placed separately in 10 per cent solutions of cresol, which cleans and sterilizes. After a few days they are rinsed in water and dried for use. The same solutions of cresol may be used repeatedly.

Discarded tubes of used mediums may be conveniently sterilized and cleaned in the following manner. With the cotton pledgets in place, the tubes are put in an upright position and left under a steam pressure of 15 lb. for one hour. All growth is thus destroyed. While the agar is still liquid, the pledgets of cotton are removed and the tubes are filled with hot water. The water dilutes the agar so it cannot again harden, and the contents of the tubes now may be safely discarded into a drain without causing trouble. The tubes require little more than a soaking in a solution of detergent, such as Soilax, and a rinsing in clear water to be ready for use again. With this technic, breakage is reduced.

Petri dishes are best sterilized separately. After sterilization, as outlined in the preceding paragraph, they are allowed to cool. The agar is then removed with a spatula and the dishes are washed with soapy water or with a solution of detergent.

If any tubes have been sealed with paraffin, cleaning them separately will prevent the filming of other glassware. If wax pencil has been used to label tubes or Petri dishes, it is preferable to remove the marks with benzene as the dishes are discarded and before sterilizing.

CHAPTER XVIII

The Direct Examination

THE purpose is to determine the presence of fungous material. In many instances this is sufficient to establish the diagnosis. With tinea versicolor and a few other mycoses, this is the sole method of confirming the clinical diagnosis. A positive result is much more valuable than a negative one, since the latter is based only on a sample and this may fail to contain fungous elements which are present elsewhere. Furthermore, treatment decreases the amount of fungous material to be seen.

The direct examination does not establish the identity of species except in certain instances, which will be described later. The reason is that in the filamentous stage usually observed, most fungi appear similar.

1. SOLVENTS AND STAINS

For ordinary routine use we have not found anything better than a 10 per cent solution of potassium or sodium hydroxide. With more concentrated solutions crystallization may occur, and this prevents or interferes with the examination. Furthermore, the more caustic solutions are hard on the hands. Other solutions which have been advocated include xylene, sodium sulfite and chloral hydrate in acacia, but there are disadvantages in the use of these and of other advocated solvents which we have tried.

A solvent which may be used when time can be allowed for clearing of the material and which offers a semipermanent specimen is an aqueous solution containing 5 per cent potassium hydroxide and 25 per cent glycerin. With this, little or no crystallization occurs and the material does not dry. In the examination of pus, when for instance actinomycosis or blastomycosis is suspected, this solution is advantageous as a solvent since the pus cells are destroyed and the fungous material becomes more apparent.

Stained slides are seldom practical for the routine demonstration of fungi which cause superficial diseases. It is difficult to hold stain with potassium

hydroxide, which tends to decolorize. The use of lactophenol, as first described by Amann and later endorsed or modified by Langeron, Linder, Henrici, Swartz and Conant, and others, is probably the best method of staining fungi in fresh tissue. The following formula is used:

Phenol crystals	20 Gm.
Lactic acid, syrup	20 Gm.
Glycerin	40 Gm.
Water	20 Gm.
Cotton blue (C 4 B Poirrier)	0.05 Gm.

The last ingredient is added after the other materials have been dissolved with gentle warming. The fresh tissue is first partially digested on a glass slide, using a 10 per cent solution of potassium hydroxide. When sufficiently softened, the preparation is flooded with water which is then removed by absorption, using blotting paper. When the hydroxide has been entirely removed, the tissue is stained by the lactophenol solution and a cover slip applied. If desired, cement may be placed around the edges of the cover slip.

When it is desired to hold for examination at a later time a slide prepared with 10 per cent potassium hydroxide, a drop of a 50 per cent aqueous solution of glycerin is placed at the edge of the cover slip. It will slowly mix with the hydroxide, producing a homogeneous mount which may preserve the specimen for several weeks or even months. Care must be used that the cover slip is not disturbed. Such a method as this is useful when one does not at first find the material which should be present or if a thorough search must be delayed.

Thin scales, such as those of tinea versicolor, erythrasma or pityriasis capitis, may be placed on a slide, washed in acetone to remove fat and mixed for three minutes with methylene blue, which is then drawn off with blotting paper. The specimen is then dehydrated with a 95 per cent concentration of alcohol and xylene and is mounted in Canada turpentine. This method gives a permanent stained mount, but it is not suitable for thick sections. Huber and Caplin use a preparation of polyvinyl alcohol, a plastic, for mounting thin tissue as well as for preserving material from cultures (see section on binding agents, Chapter XXIV, p. 262).

2. MAKING THE PREPARATION

Place the material on one end of a clean glass slide and add a small drop of a 10 per cent solution of potassium hydroxide. Put on a cover slip and add almost enough hydroxide to fill in the space between the cover slip and the slide. Pass the slide through the flame of a Bunsen burner three

or four times. Examine it under the microscope. If the preparation is not clear, reheat it and examine it again. Repeat this until the tissue is clear enough to provide satisfactory examination. The material is placed on one end of the slide so that the fingers are not burned when the slide is being heated, and the potassium hydroxide is added cautiously to avoid flooding.

As an alternative method if an immediate examination of the mount is unnecessary, the prepared slide may be left warming over a microscope lamp. This prevents disorganization of the tissue to be examined. Care should be taken that evaporation does not cause crystallization. If the slide becomes dry, water may be added, rather than more hydroxide, so that the crystals are redissolved.

Many other methods and reagents have been described. Reports of some are mentioned in the bibliography.

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CHAPTER XIX

Appearance of Fungi on Direct Examination

THE various Hyphomycetes which cause infections may be seen in the skin or its appendages either in the filamentous or in the spore stage. In the earliest phase of the infection the filamentous form is noted exclusively. Later, spores are observed, and in older infections they predominate. We have thought it best to describe the findings in the sections on the various tissues.

1. HAIR

Filaments are rarely noted except in hairs infected with A. schoenleini. Spores vary in size, being largest in the endothrix Trichophyta (T. violaceum, T. crateriforme, T. sulfureum). The hair shaft may be noticeably invaded when infection is due to these micro-organisms and less so when it is due to one of the Microspora (such as M. lanosum or M. audouini). With the last-mentioned fungi, the spores are present in the sheath of Henle, externally to the hair shaft. The position of the spores (whether they are external to or are invading the shaft) may sometimes be determined in a freshly made specimen, before the hair becomes too flattened, by moving the objective up and down.

The appearance of infected hair may be noted in the accompanying illustrations. The predominant infections in hairs are caused by several Microspora. With these, small round spores in mosaic form are seen on the shaft of the hair. In the endothrix infections, the spores are usually seen in linear formation, since they are derived from the filamentous stage by segmentation. When the infection is due to A. schoenleini, the amount of material is less than with other infections, and filaments, which may be irregularly segmented, are commonly observed. In addition, air bubbles are often present. Because of this characteristic picture, favus may be

recognized on microscopic examination. In ectothrix infections (T. gypseum, T. niveum, T. purpureum), the spores are of medium size and occur in irregular groups, compact or loose, outside the hair shaft. We seldom see follicular infections due to ectothrix.

2. SCALES

With tinea glabrosa the fungus is usually present in the scales as filaments (Fig. 69). If the infection is of long duration, numbers of spores may be noted. It should be mentioned here that spores may be readily confused with artefacts such as oil droplets.

With tinea versicolor there are groups of spores (double-contoured) and numerous filaments which readily become segmented (Fig. 88).

When scales from lesions of tinea cruris are removed and examined, filaments or spores in chains are seen. If the infecting micro-organism is E. inguinale, the elements are large. The number of elements present in a specimen may vary, but with E. inguinale the number is usually greater than with T. purpureum or T. gypseum.

3. MACERATED SKIN

The appearance of T. gypseum, T. purpureum or E. inguinale is similar to that noted in scales; i.e., the fungus occurs as chains of spores. Monilia albicans is sometimes revealed as clusters of spores and nonseptated hyphae.

4. ROOFS OF VESICLES

Here again septate mycelium or chains of spores may be noted, sometimes in profusion. It is in this tissue particularly that one is apt to note mosaic fungi, the exact nature of which is as yet imperfectly understood (see the section on artefacts, Chapter XX, p. 246).

5. NAIL TISSUE

In leukonychia trichophytica, fungi are noted on the surface of the nail. When there is overlapping of toes, the nail on which an adjacent toe rests is frequently infected. In other infections due to T. gypseum and in those due to T. purpureum the infection is often seen in the deeper part of the nail. One may observe hyphae similar to those noted in scales, macerated skin or the roofs of vesicles. These seldom branch; the elements are fairly homologous, and they are not seen in a tangled network. Many spores may

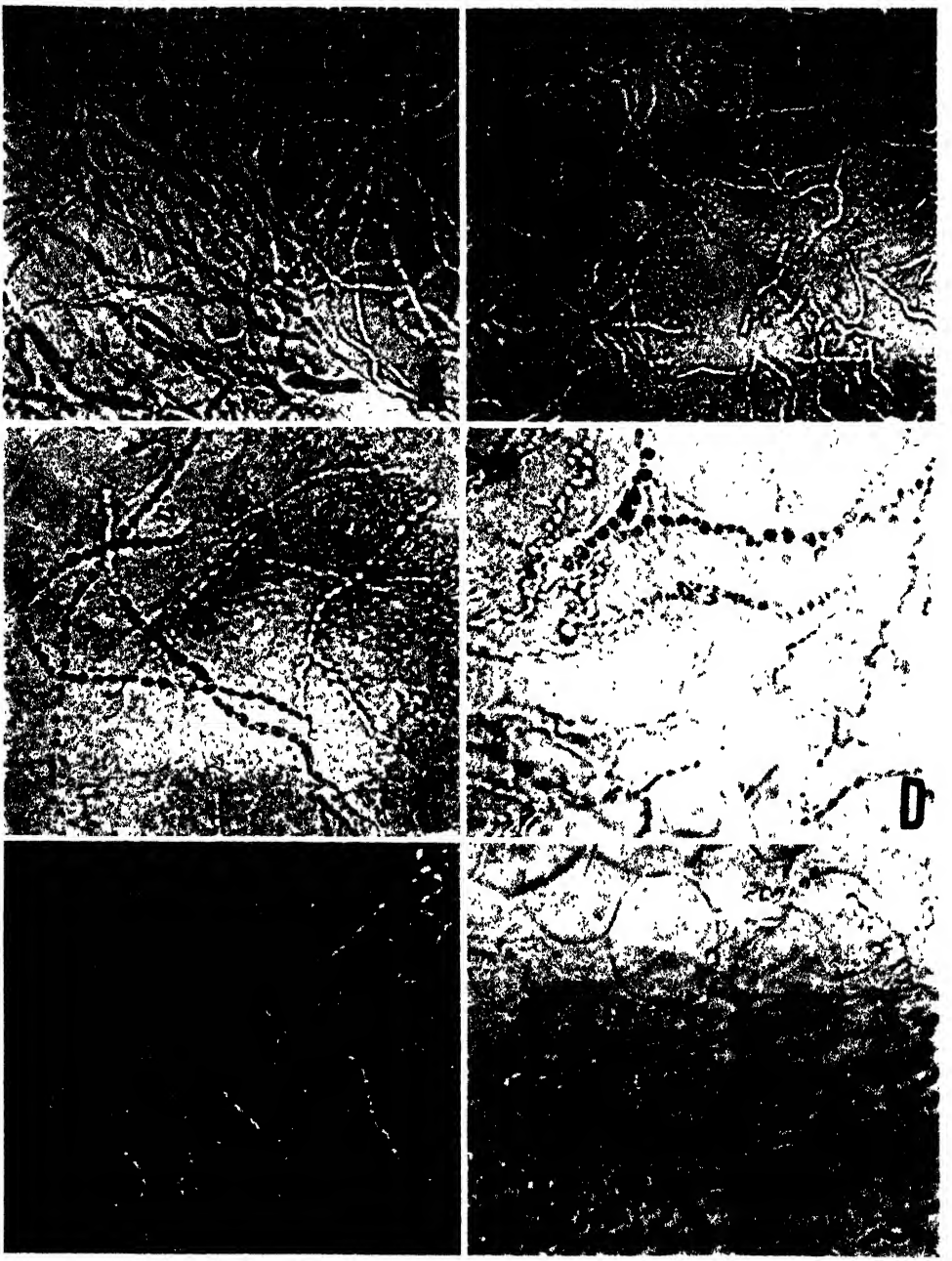

FIG. 69. Appearance of ringworm fungi in scales, roofs of vesicles, macerated tissue or nails. *A* and *B*, hyphae showing no septations, as frequently seen in infections of short duration. *C* and *D*, sporulated mycelium characteristic of infections of longer duration and commonly noted with tinea unguium; × 400. *E* and *F*, short filaments, the result of disintegration.

be present. One rarely observes the fructification bodies which are seen when pathogenic fungi are cultured on artificial mediums. After treatment, nail tissue may be the only available source of infected material in which fungi can be demonstrated.

In nails invaded by M. albicans, when the marginal discolored and undermined tissue is examined, clusters of round cells in mosaic pattern are to be found. Filaments are rarely seen. Oil droplets must be differentiated from the yeastlike cells.

6. PUS

When material from the contents of superficial pustules or blebs is examined, fungi are rarely found. Pus aspirated from deeper lesions or removed from a discharging sinus should be examined for the structures of one of the fungi which produce granulomas. Granules or noticeable small clumps of organisms may be quickly observed when a drop of fresh pus on a slide is covered with a cover slip. They usually denote an Actinomyces. Sporotrichum schencki is difficult to demonstrate in direct preparations. The budding micro-organism of Blastomyces and the endospores of Coccidioides may be found. More detailed descriptions will be found in the section on the various deep mycoses.

7. SPUTUM

The direct examination usually is not reliable, even if the specimen is centrifuged, since contamination is hard to eliminate. However, Actinomyces bovis and M. albicans are both recognizable in the forms in which they appear. It is well known that fungi are notorious as secondary invaders in pathologic tissue. As such, they may also harm the host. Cultural studies followed by critical analysis and correlation with clinical facts are here doubly advisable. Dickson has shown that C. immitis is not uncommonly observed in the sputum of patients in the San Joaquin Valley of California who have a febrile pulmonary disorder.

8. FECES

In routine examination for M. albicans, cultural technic alone is generally used. If care is taken that the specimen is not contaminated with air-borne fungi, there is usually no difficulty in obtaining a growth of M. albicans. Bacteria in the specimen do not grow well on acid dextrose agar at room temperature.

9. BLOOD

In searching for H. capsulatum both stained and unstained mounts should be examined. The micro-organism is usually found intracellularly.

10. STAINED SECTIONS

Sections of pathologic specimens from lesions in the skin or in other organs may reveal fungi of many different species. If one is trained in observing the appearance of unstained slides, the staining characteristics and the shrinking of the specimen are apt to cause difficulty in recognition of the fungus. Practice will overcome this difficulty, although one may hesitate to make a definite diagnosis from a given slide. Structures such as those observed in blastomycosis or coccidioidomycosis are characteristic even in stained preparations.

CHAPTER XX

Dubious Fungous Forms and Artefacts

THE forms to be described will be observed fairly frequently, and their appearance should be readily learned.

1. THE MOSAIC FUNGUS

The majority of those who have examined many scrapings have expressed the opinion that the so-called mosaic fungus (Weidman) is an artefact. Stumpf claimed that the mosaic fungus is made up of free fatty acids. Davidson and Gregory stated that the mosaic fungus consists of cholesterol crystals; Cornbleet and his co-workers agree with this observation on the basis of their experiments using fluorescence microscopy. Some still hold that it is a degenerate form of a pathogen. Dowding and Orr reviewed the literature and cited their own experiments as evidence that the mosaic fungus is transformed from T. gypseum. They have observed (as we have) that ordinary hyphae and mosaic segments are occasionally to be seen in apposition; that normal spores and hyphae are sometimes part of the mosaic formation, and that the amount of mosaic material increases while the numbers of living fungi decrease during the healing of lesions.

The appearance of the mosaic form was described by Weidman as follows:

> The segments are irregularly shaped, and are separated from each other by narrower or broader, but definite spaces; they have a moth-eaten appearance, and their edges and corners are rounded off. They do not have any organized internal structure; arthrospores are not visible within the segments. But it is the arrangement of the mycelium that raises the question whether this is fungus—not so much that it occurs in smaller and larger patches, but that the mycelium ramifies and anastomoses around the individual epidermal cells in such a way as to suggest that air or other refractile matter had become imprisoned between the cells. These hyphae vary in width, until finally one recognizes only threadlike filaments coursing between the cells. It requires fine discrimination to come to the conclusion that these are fungus and not inert inter-

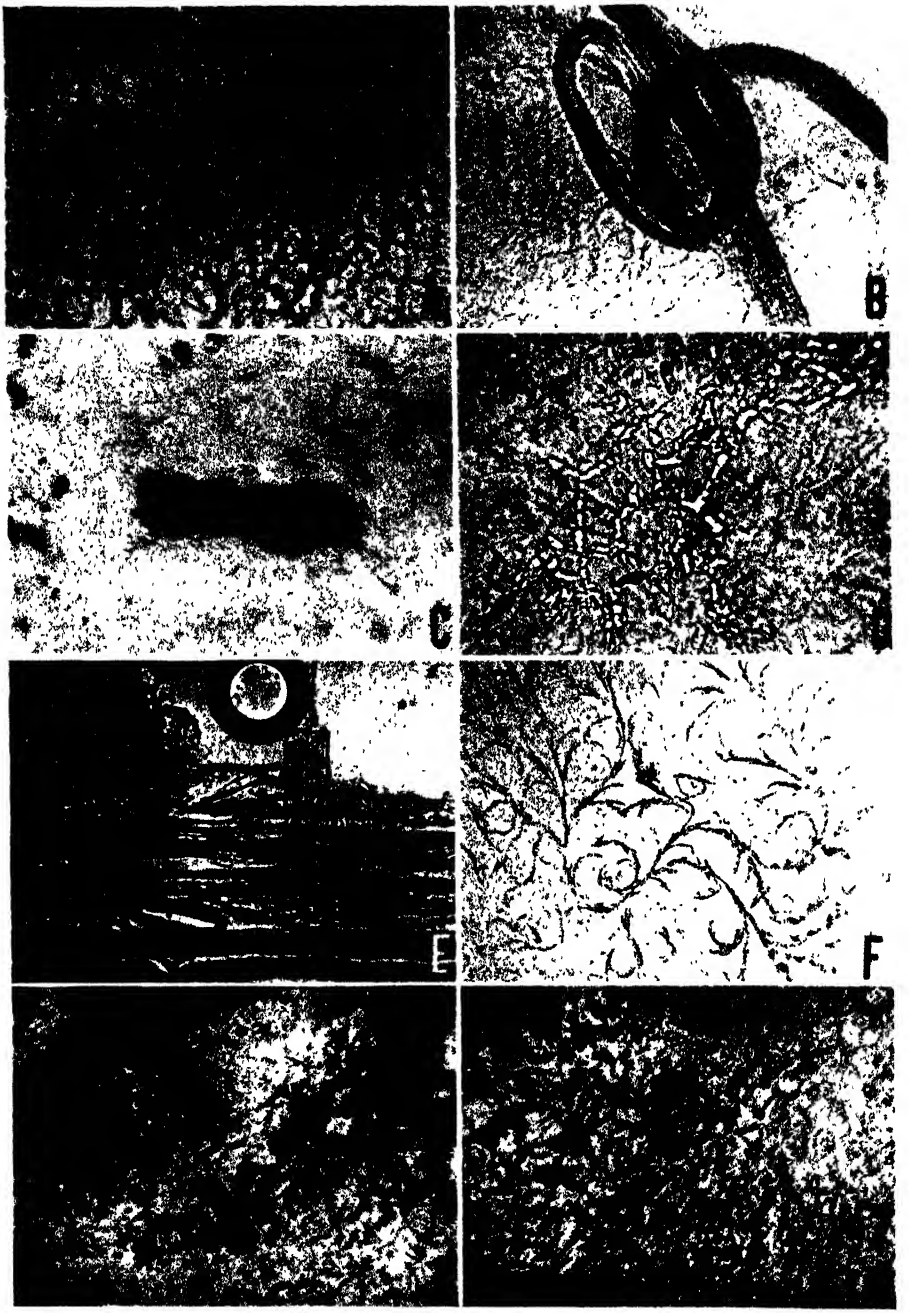

FIG. 70. Foreign material frequently found in skin scrapings. *A*, cotton fiber. *B*, wool fiber. *C*, plant fiber. *D*, mosaic fungus, the exact nature of which is in dispute. *E*, wood fiber and air bubble. *F*, crystals of potassium hydroxide which have dried on the surface of the cover slip. *G*, amorphous débris from lesions treated with zinc ointment. *H*, oil globules, which may simulate fungus spores.

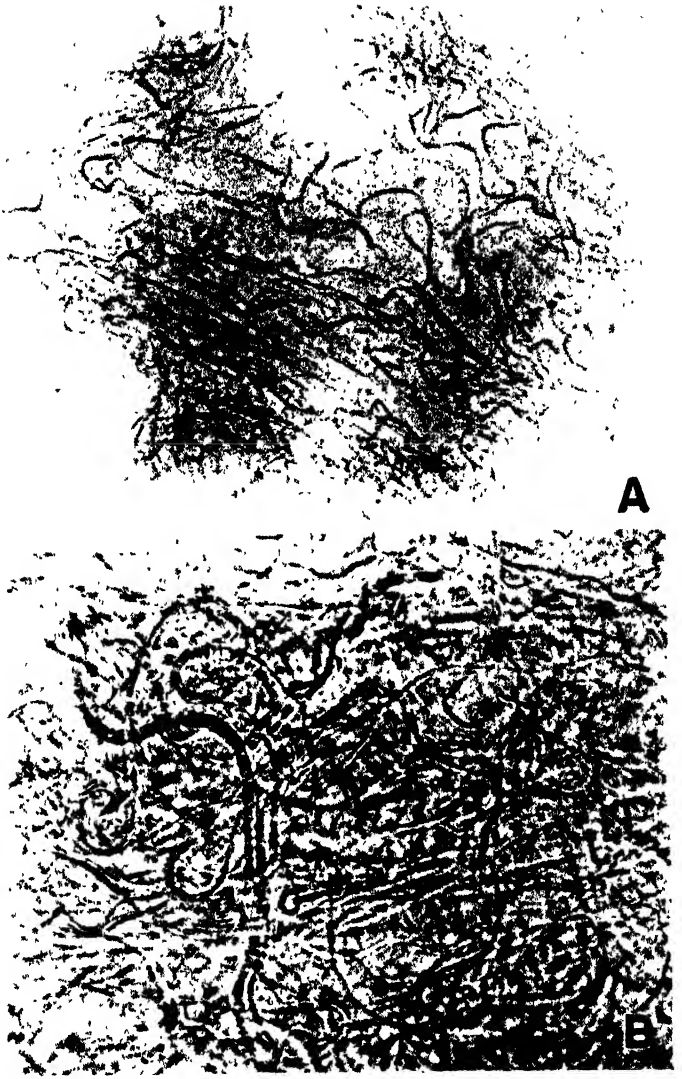

FIG. 71. Elastic fibers present in a deep section of skin or in pus may be confused with hyphae (see text, p. 246). Magnification: *A*, × 220; *B*, × 480.

cellular accumulations. I have applied the term "mosaic" to this form because, following as they do the intercellular clefts, the hyphae come to surround smaller and larger polyhedral spaces, which collectively give the "pavement" effect.

The remarkable fact that this form is seen only in locations and usually in lesions suggesting a fungous origin has not yet been satisfactorily explained. In lesions equally inflammatory or in scaly conditions of the skin remote from the hands and feet it is seldom isolated. Thus in the scales of psoriasis, pityriasis rosea, or seborrheic dermatitis, the mosaic form is unknown. The mosaic fungus may indicate a fungous infection without being of definite fungous structure.

2. SAPROPHYTES

If the amount of vegetative fungous material is large, if there is branching, if there is a green or brown tone or if the individual segments are large or of different sizes, one is fairly certain that the fungus is not a pathogen. Judicious selection of material after one discards superficial scales or nail tissue will usually obviate the necessity of deciding whether the fungus is a saprophyte or a pathogen. In open lesions, particularly those of long duration, saprophytic fungi may colonize in the diseased tissue and will perhaps produce clinical symptoms.

3. ARTEFACTS

Oil and grease, air, hairs, cotton fibers, feathers and many other substances may cause trouble for the novice. One should mount specimens of various artefacts and become familiar with their appearance. The variations in size of the oil droplets or air bubbles stand out in contrast to the relative uniformity in size of spores or yeast cells. With structures such as cotton fibers, examination of the ends will show a ragged or square effect, whereas a fungous filament is always rounded at its ends. Green and Shepard drew attention to the possible confusion with elastic fibers when the specimen is a shaving of skin extending into the cutis. Elastic fibers may be observed at times in pus. The profusion of fibers, the absence of cross-walls, their translucency and the variability in size serve to differentiate them from fungi.

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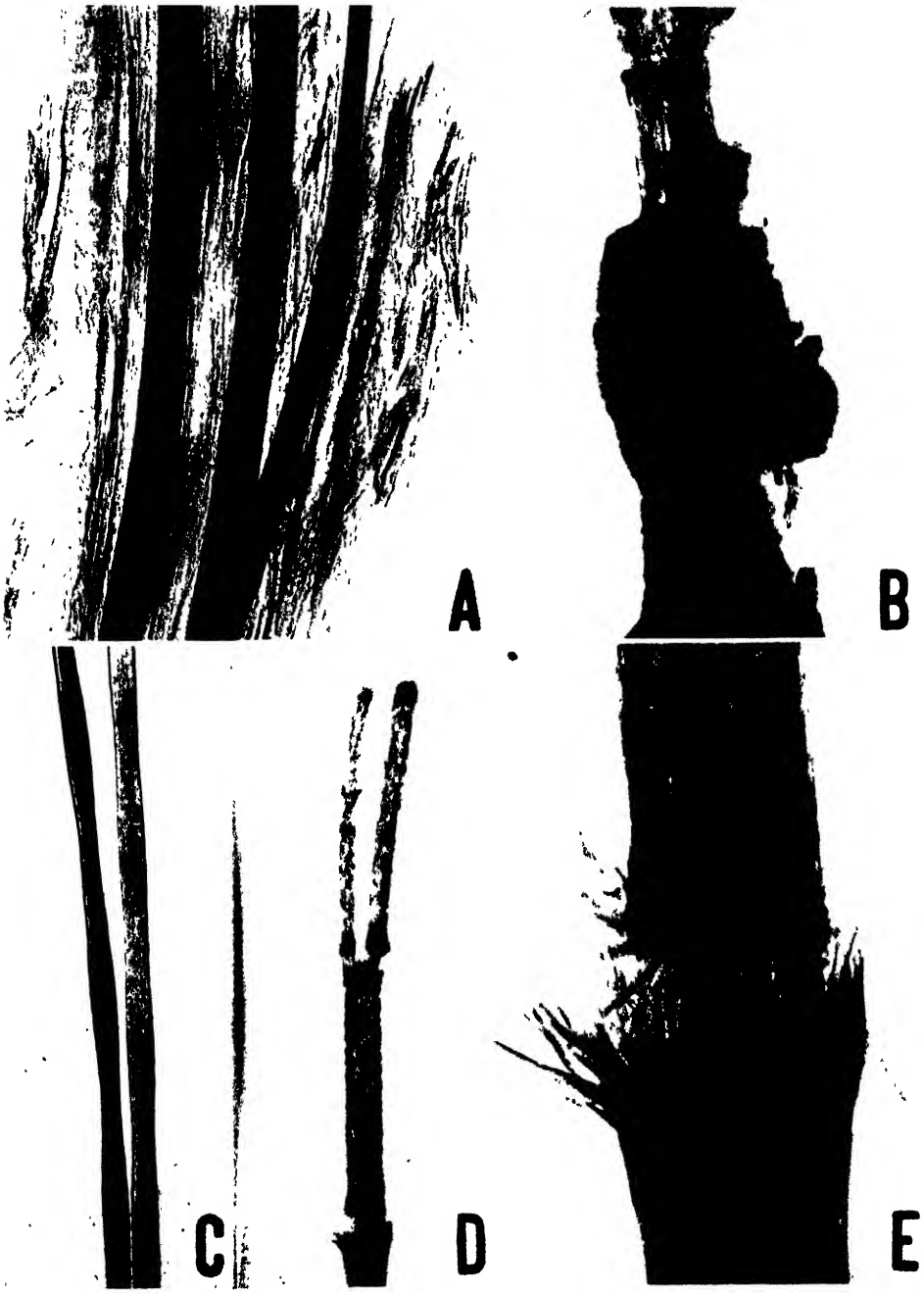

FIG. 72. Nonmycotic hairs. *A*, tinea amiantacea; × 56. *B*, lepothrix; × 108. *C*, monilethrix; × 56. *D* and *E*, trichorrhexis nodosa; × 52 and × 230, respectively.

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CHAPTER XXI

Cultural Methods

WHEN one wishes to determine the species of infecting microorganism, it is necessary to study its appearance and behavior on artificial mediums. We believe that in the future cultural methods will be more generally employed for the isolation of pathogenic fungi. The routine technic is not too difficult for the practicing physician. Throughout this book we have pointed out many times the obvious advantage of a precise diagnosis. The type of treatment may depend entirely on the cultural findings. It is indisputable that the patient will nearly always benefit from the exact knowledge to be gained from cultural studies. Physicians are greatly indebted to Sabouraud, who established the pathogenic nature of many species of fungi. He found that a culture medium which consisted of French maltose (imported from Germany), Chassaing peptone and agar supported growth of most fungi when they were incubated at room temperature. He further demonstrated that there was a remarkable uniformity in the gross cultural appearance of any given species of fungus and that this was sufficient for its recognition in the majority of instances.

During World War I, maltose could not be obtained. The limited supply on hand was soon exhausted, so substitutes were used, with varying success. Weidman and McMillan showed that crude American dextrose could be used as a satisfactory substitute for maltose. Weidman and Spring found that 16 of 18 species of fungi which they tested produced satisfactory growths when Fairchild's peptone (an American product) was substituted for Chassaing peptone (a French product). Hodges also found Fairchild's peptone suitable for use. Numerous synthetic mediums have been proposed; in theory, a medium in which the exact chemical constituents are known is to be desired. Neither dextrose nor peptone is of constant composition; minor variations in the medium often result in changes in the characteristics of a fungous colony. Weidman and Spring rightly stated that such a medium must prove its superiority over those now in use by being

as differential as Sabouraud's test medium, internationally available and comprised of ingredients which will not vary from year to year. The work of Williams and Southworth indicates that such a standard medium may soon be in common use. For the present, the mediums listed in the following pages are recommended for routine use.

It should be emphasized that only certain sugars are suitable for inclusion in the formulas of mediums. Development of color in a colony or in the adjacent medium may be an important feature of the fungus. We have found that the carbohydrate component of the medium is the fraction used by the fungus for this purpose; most monosaccharides can be utilized, but disaccharides, such as maltose and lactose, and other complex sugars cannot be used by fungi to form pigment.

Stock cultures may be kept on an ordinary medium until moderate growth has taken place and may then be stored in the refrigerator. To prevent contamination in handling and to lessen the drying of the agar, the top of the tube should be covered with cellophane kept on with a rubber band. We have found cellophane better than tin foil or wax paper, as it is transparent and labels or crayon marks may be seen through it without its being removed. In addition, cellophane is punctured less easily than tin foil when one is handling the tubes. Under the conditions described, colonies may be kept for three to six months.

The addition of yeast extract powder to standard medium enhances the features of the fungus, such as the formation of spores, characteristic color and contour. It seems to reduce the tendency for the organism to become pleomorphic.

1. FORMULAS

The artificial mediums needed for routine use are not numerous. The following kinds are useful.

DEXTROSE AGAR

This preparation is intended for routine use in the isolation of fungi. The only difference between this formula and that of Weidman's Pennsylvania medium is the substitution of Difco peptone for Fairchild's peptone and technical dextrose for the crude American variety, both changes being without discernible sacrifice of any advantage.

Agar (granular)	18 Gm.
Peptone (Difco)	10 Gm.
Dextrose (technical)	40 Gm.
Distilled water	1,000 cc.

The pH is usually 5.8 to 6.2, although it is not necessary to be particular about this.

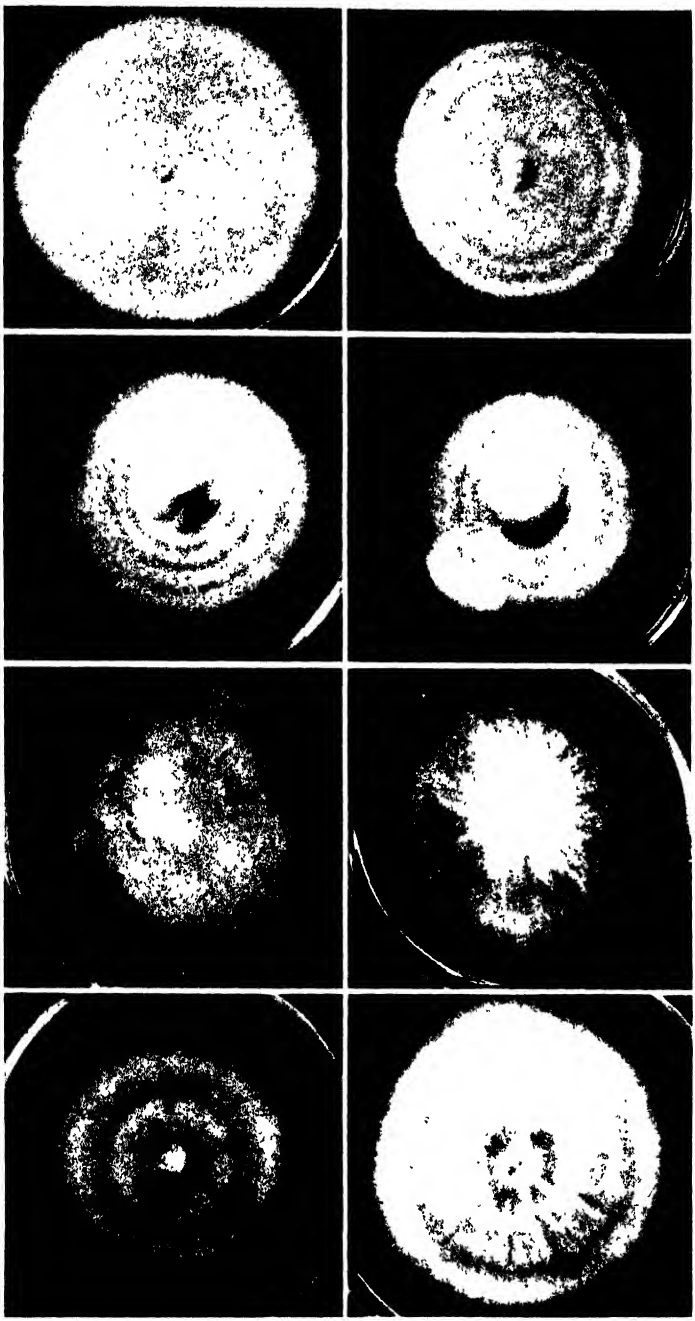

FIG. 73. Comparison of cultural growths when one of two different sugars was used. The mediums in the plates on the left contain technical dextrose and those on the right contain technical maltose. The organisms, from the top down, are T. gypseum, T. purpureum, M. lanosum and M. audouini. All the growths are 1 month old.

1. Add the agar to 700 cc. of the water and soak for one hour.
2. Add the peptone and dextrose to the remaining 300 cc. of water. Stir for a few minutes until both ingredients are dissolved.
3. Cook the agar and water in an aluminum pot, stirring occasionally.
4. When the agar is almost dissolved, start to cook the peptone and dextrose mixture; stir.
5. When both the agar and the peptone and dextrose are dissolved, add the peptone and dextrose to the agar and stir.
6. Measure the mixture into test tubes.
7. Autoclave the tubes for 20 minutes at a pressure of 15 lb.
8. Slant the tubes and leave them until the medium is solid.

DEXTROSE BROTH

A liquid medium of simple structure may be useful in studying yeastlike fungi, to flood certain growths on a solid medium or in the preparation of massive growths for use in making extracts.

Dextrose (crude American)	40 Gm.
Peptone	10 Gm.
Distilled water	1,000 cc.

The method used in making dextrose agar should be followed.

CONSERVATION AGAR

This was advocated by Sabouraud to prevent the loss of the character of the colony through excessive vegetative growth. We find that unless one is careful the colony may die because of slowness of growth on the conservation medium. The method of making conservation medium is similar to that of the ordinary dextrose agar, the only difference being the omission of dextrose from the former.

Agar	18 Gm.
Peptone (Difco)	10 Gm.
Distilled water	1,000 cc.

If desired, 20 Gm. of technical maltose may be included. The colony is then neither too luxuriant nor too scanty and the characteristics of the culture remain constant.

CORN MEAL AGAR

This is used in the differentiation of various species of Monilia and Cryptococcus. It is also useful when one is studying the spore forms of the dermatophytes. Its value is partly due to a minimal nutrient content; the growth, while scant, shows the characteristics of fructification.

Yellow corn meal	40 Gm.
Agar	15 Gm.
Distilled water	1,000 cc.

1. Add the corn meal to 500 cc. of water and keep heated to 65 C. for one hour. Filter through paper.
2. Dissolve the agar in the remaining 500 cc. of water by heating.
3. Mix the corn meal and the agar.
4. Filter through cotton. This is a slow process, and the agar will cool and harden unless the flask is placed in a steam bath or sterilizer.
5. Measure the mixture into test tubes.
6. Autoclave the tubes for 20 minutes at a pressure of 15 lb.
7. Slant the tubes and leave them until the medium is solid.

POTATO-CARROT AGAR

This agar is useful in demonstrating the color characteristics of a colony.

Carrots	20 Gm.
Potatoes	20 Gm.
Agar	15 Gm.
Distilled water	1,000 cc.

1. Wash and peel the vegetables and cut them into small pieces, then add them to 700 cc. of water and boil the mixture down to 500 cc. Filter through paper.
2. Dissolve the agar in 500 cc. of water by heating.
3. Mix the vegetables and the agar.
4. Measure the mixture into test tubes.
5. Autoclave the tubes for 20 minutes at a pressure of 15 lb.
6. Slant the tubes and leave them until the medium is cooled.

WORT AGAR

This commercial medium, a Difco product with a pH of 4.8, is a good substrate for the isolation and differentiation of the yeasts and yeastlike organisms, as it almost entirely eliminates the growth of bacterial contaminants. This is due to the high hydrogen ion concentration, which, while not harmful to yeastlike fungi, inhibits the growth of bacteria.

WORT AGAR ENRICHED WITH FAT

To freshly made Wort agar, a sufficient quantity of ether extract of crude lanolin or butter is pipetted over the surface and allowed to dry. Benham recommends this agar for the isolation of Pityrosporum ovale.

ANAEROBIC MEDIUM (BREWER)

This medium is chiefly used to isolate Actinomyces.

Pork infusion solids	1.0 Gm.
Peptone (thio)	1.0 Gm.
Sodium chloride	0.5 Gm.
Sodium thioglycollate	0.1 Gm.
Agar	0.05 Gm.
Water	q.s. ad. 100.0 cc.

To this basic formula may be added:

Methylene blue	0.0002 Gm.
Dextrose	1.0 Gm.

The methylene blue is an indicator; the dextrose is for enrichment.

This medium may be obtained from Baltimore Biological Laboratory, 432 North Calvert Street, Baltimore.

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2. INOCULATION OF MEDIUM

The area of skin from which material is to be taken is washed with 70 per cent alcohol. Then it is scraped with the blade of a sterile scalpel, and the material is transferred directly to the agar slant. The material is left on the surface when the scalpel is cut several times across the medium. We use this method for the culture of macerated skin, scales, nail tissue, material from a moist, exuding surface and hair from the scalp. Hair can probably be best removed from the beard by epilating forceps. When hair is removed for the direct examination, a forceps is usually employed so that the entire hair can be examined. The scalpel scraped over the tongue gives one a good specimen from the mouth. Transferring the material immediately from the patient to the agar gives a high percentage of cultures free of contamination.

A platinum loop of medium strength is useful in transferring a specimen of stool to the surface of the agar slant. The same implement is useful in transferring specimens of serum, spinal fluid, bile or sputum from specimen bottles. Here it may again be emphasized that fresh material is desirable, since most normal and pathologic body fluids are good mediums for the

incubation of fungi, and small foci of contaminants, which might be disregarded at first, are soon found in such massive quantities that they erroneously impress one as being of pathogenic titer.

Pus is transferred by means of a sterile syringe or a flamed platinum loop, if the lesion is open. The material should be placed near the center of the agar slant. The mouth of the tube may be flamed over a Bunsen burner after the cotton is taken out, before and after inoculation. We have not found that this procedure reduces the incidence of contamination, so we have discarded it as unnecessary and burdensome.

Care should be taken that the cotton plug is not contaminated while the inoculation is being made. For instance, it must never be laid down. It should not be withdrawn until the material is on the blade of the knife and is reinserted as soon as the inoculation has been completed.

Contamination starting at the upper pole of the agar slant or away from the line of inoculation usually has originated from the outside, while the tube was open. If contaminating organisms appear near or in the lines of inoculation, they have probably been carried into the tube in the substance of the inoculum.

To culture Actinomyces from material in which granules are present, add a large volume of saline and shake. The granules settle. The supernatant fluid is drawn off. The granules are washed a second time and are then drawn up into a sterile pipet and transferred to the depth of the anaerobic medium.

CHAPTER XXII

Characteristics of Fungi on Culture

SPECIES of fungi may usually be recognized by their cultural appearance. With experience one may recognize many species, as one would a human acquaintance, without having to see all the features. At other times, particularly when variants appear, all the characteristics of the micro-organism may be required in order to determine its nature.

The information to be mentioned in this chapter will usually suffice for diagnosis. It is well to examine the inoculated culture medium after two or three days (to see if contaminating organisms are present), after five to seven days (for the early characteristics) and finally after 10 days to three weeks (for the characteristics of the full-grown prime colony).

1. ROUTINE EXAMINATION

1. The date of inoculation should be placed on the label of the culture tube together with some means of identification. When the colony is examined, the age may then be readily determined.

2. The kind of medium used should be noted. It may again be emphasized that even slight differences in the composition of the medium may alter the cultural appearance. On growths sent to us for identification, we often find it necessary to transfer the culture to our own standard medium to develop the characteristics of the colony with which we are familiar.

3. The number of days before growth is first noted is significant.

4. Rapidity of growth is indicative. If a colony is at prime in seven to 10 days it may be considered a fast grower; if three weeks elapse before it can be recognized, it is a slow grower; most fungi are of intermediate character. The rate of growth is influenced by many factors, such as temperature, the depth of the agar and the type of culture medium. In the summer the rate of growth of fungi is noticeably faster than during the winter months; the greater the depth of agar the faster and more luxuriant

the growth; culture mediums containing dextrose or other nutrient substances support more vigorous colonies than starvation mediums without these substances.

5. The luxuriance of growth is characteristic. Fungi differ in their capacity to develop. One fungus covers the entire surface of an agar slant within two weeks; another fungus, such as A. schoenleini, never covers more than a small portion. Weidman pointed out that there is a difference between volume and luxuriance of growth, although the two are usually seen together. The same factors which influence the rate of growth also affect the character of the colony.

6. Surface configuration aids diagnosis. The gross topographic characteristics of colonies (probably due in part to inequalities in growth) vary considerably. A colony may be flat, rounded, fissured, cerebriform, umbilicated, folded or concentrically ringed. More than one feature may be present in the same colony. Changes in the composition of the medium may affect the gross appearance of a colony. The depth of the agar influences the appearance; this can be seen when a growth is present along the entire length of an agar slant where there is considerable variation in thickness. In general, the depth of agar required for mycologic specimens is greater than that used ordinarily in bacteriologic technic.

7. The margin of the colony may be sharply defined or may fade into the medium.

8. The texture of colonial growths of fungi varies a good deal. One observes a downy or filamentous growth when the vegetative aerial mycelium predominates and is loosely arranged. If the mycelium is closer together, the growth appears compact or velvety. A granular surface is due to the presence of spores. A pasty surface denotes a yeastlike micro-organism, and a waxy appearance is characteristic of A. schoenleini.

9. The color both of the colony and of the medium is occasionally an important feature. A violet hue of the colony of T. violaceum is characteristic. The typical port-wine stain of T. purpureum rarely appears in the growth until after two or three weeks. Pigment usually appears first on the under side of the colony. A brownish discoloration of the medium is observed with many different fungi. Many fungi lose their colors after repeated subcultures. The character of the culture medium is important, since some mediums (like potato) will demonstrate pigment that ordinarily is not present.

10. Submergence of the colony is seen in cultural growths of A. schoenleini and of several other fungi. Splitting of the medium (due to the wedge of growth) is not uncommon in old, compact growths.

The same strain of fungus is subject to a range of variation in cultural

appearance which may be due to temperature (season), moisture, or other factors. It is difficult to obtain a characteristic colony of T. violaceum or T. crateriforme during the winter months. In winter the early growth of different strains of T. purpureum is fairly uniform, but in summer considerable variation in the gross cultural characteristics is common.

2. PLEOMORPHISM

After prolonged isolation on a culture medium, many fungi assume a vegetative character, as evidenced by a white fluffy growth almost always starting at the point of inoculation. Within a short time the entire colony may be covered. Some fungi, such as M. lanosum, develop this character after a short time, while other fungi, such as T: violaceum, never assume the vegetative form. This result of degeneration, old age or monomorphism, whichever it may be, is difficult to overcome once it has appeared. Subculturing sometimes causes the micro-organism to assume its original nature, but in such instances the growth is probably not truly pleomorphic. It has been suggested by Sabouraud, Catanei and others that this state may be present in a primary culture; thus T. interdigitale is considered by some to be a degenerate form of the granular type of T. gypseum. We believe T. interdigitale is a variant of T. gypseum. The development of pleomorphism may result in a loss of virulence, as evidenced by the degree of involvement of infected tissue. Catanei has performed experiments substantiating this.

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CHAPTER XXIII

Preservation of Fungus Colonies

1. REASONS FOR PRESERVATION

THE span of time during which a fungus in culture is at prime varies somewhat with the species. In most cases it is short. Thus most pathogenic growths require two or three or more weeks to attain maturity and may be at their best for only a week or 10 days. In order to keep a display of fungi in culture and also to give our students a representative collection of typical pathogens, we evolved a practical method by which a fungus colony may be preserved in its typical form for an indefinite period. The gross appearance of the colony remains unchanged for many months. Under filtered ultraviolet rays, however, the color becomes noncharacteristic and dull as soon as the growth is killed. This procedure eliminates all danger of accidental human inoculation, an important consideration with virulent fungi such as C. immitis.

2. METHOD OF PRESERVATION

The fungus is inoculated on a medium which has dried out somewhat, as excessive moisture prevents the development of a radial colony. When the colony has acquired a characteristic appearance, the cotton pledget is moistened with 10 drops of a 40 per cent solution of formaldehyde and replaced in the test tube. After 24 hours the pledget is trimmed off even with the test tube and dipped in paraffin to make a completely air-tight seal. This latter precaution is necessary to prevent evaporation of moisture from the agar, with resultant shriveling of the fungus growth

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CHAPTER XXIV

The Culture Mount

IN ORDER to identify species of fungi, it is often necessary to study the character of their spores and their arrangement. These are characteristically formed in the aerial portions of the colony. It is impracticable to study the colony directly under the microscope because of the density of the growth and because the margin of the colony, where it might be viewed, is entirely vegetative. If portions of a colony are removed and mounted there results great disruption in the arrangement of the material. However, characteristic spore forms may often be demonstrated in this way. If mounts are made from a subculture on corn meal agar where the vegetative growth is reduced, the direct mount is more satisfactory. A hanging-drop preparation, in which the fungus is grown in a drop of liquid medium in an enclosed space, has the disadvantage of a limited air supply, which modifies the growth so that the vegetative structures predominate. With the two methods to be described, the first of which we owe to Henrici, the nature of spore forms may be satisfactorily studied. The first is additionally valuable since permanent stained mounts may be made.

1. COVER SLIP METHOD

Step 1. Moistened filter paper or a damp blotter is placed on the bottom of a Petri dish and sterilized in an autoclave at a pressure of 15 lb. for 20 minutes.

Step 2. Six cover slips are cleaned, flamed and placed on the moist blotter or filter paper.

Step 3. A special medium is required. We use one containing 2 per cent dextrose, 0.5 per cent peptone and 2 per cent agar. The medium must be filtered through paper in order that any foreign particles may be removed before sterilization. It is then melted, cooled to between 40 and 50 C. and inoculated with spores of the colony to be studied. It should be well shaken in order that a uniform suspension may be obtained.

Step 4. With a loop needle, a thin layer of the inoculated agar is spread over the surface of the cover slips.

Step 5. The organism is incubated at room temperature. When sufficient growth has taken place, the cover slips may be removed with flamed forceps.

Step 6. For immediate study and temporary preparations, the cover slip may be inverted on a drop of water on a slide and immediately examined.

Step 7. For a permanent mount, the air bubbles are removed by addition of alcohol (95 per cent). The alcohol is drained off and a drop of lactophenol is added with cotton blue. The cover slip is allowed to stand for two minutes and then inverted on a microscope slide. After two or three days, excess mounting medium is removed and the preparation is sealed with asphalt varnish.

For alternative methods to improve the seal (1) use the double cover slip method, with the lactophenol cotton-blue mixture between cover slips of dissimilar size, and after two to three days mount in clarite, which does not turn yellow on standing; (2) allow the culture to dry, stain and mount in clarite.

2. CULTURE CHAMBER METHOD

With this method, which is a modification of Henrici's culture chamber method, the aerial portion of the colony may be studied independently of the vegetative part.

Step 1. A thin layer of dextrose agar is poured into a sterile Petri dish and allowed to harden.

Step 2. With a flamed hooked needle a hole is made through the agar, the cut portion being discarded. The hole may vary in size or shape but must be smaller than a cover slip.

Step 3. The pathogenic fungus to be studied is inoculated at three or four points on the rim of the hole.

Step 4. A cover slip is placed over the hole, a small part being left uncovered to admit an adequate supply of air.

Step 5. Progress of the growth can be determined by viewing the growth through the back of the Petri dish without opening the chamber. When the culture is sufficiently developed, the lid of the Petri dish is removed. This exposes the medium to outside contaminants, which may interfere with prolonged study.

3. WET INDIA INK PREPARATION

Weidman and Freeman called attention to the value of a wet India ink preparation in the differentiation of yeastlike growths. They advocated

the following technic: "A loopful of India ink is placed on a glass slide, and a loopful of the culture material is quickly emulsified in it. A large coverslip is quickly applied and pressed gently." Practice is necessary in order to bring out the halo effect (in T. histolytica). Three precautions are essential: the preparation must be made quickly; the drop of fluid must be small; no previous mounting material, such as hydroxide, glycerin, alcohol or stain, may be present.

4. BINDING AGENTS

(a) ASPHALT VARNISH.—This is a durable agent, which does not chip. After a long period there may be some separation. Use while fresh. It may be obtained from any biologic supply house. In New York City, Eimer and Amend carry a satisfactory product.

(b) DUCO CEMENT.—This is preferred by some. A seal is quickly attained. There is a tendency to brittleness, and adherence may not be as reliable as with other agents.

(c) CLARITE.—A newer product with which we have not had much experience.

(d) POLYVINYL ALCOHOL.—This may be mixed with phenol, lactic acid and cotton blue. According to Huber and Caplin, it is said to clear and dehydrate as well as to provide a permanent hyaline mount.

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CHAPTER XXV

Microscopic Characteristics of the Dermatophytes

WHEN specimens of a fungus colony are examined, various vegetative and reproductive forms may be distinguished. Only vegetative forms are seen at the periphery of the colony; the spores (reproductive) are to be found toward the center or at the base. These microscopic features are dissimilar in different genera, and frequently there are minor variations in species. The variations, however, may result from conditions of growth rather than arise as specific characteristics. In most instances the gross appearance of a colony is sufficient to identify the micro-organism provided the observer is familiar with the medium on which the fungus is growing. Confirmation of the cultural diagnosis is the chief purpose of the culture mount in routine practice.

1. VEGETATIVE FORMS

(a) MYCELIUM, HYPHAE AND THALLUS.—These terms indicate threadlike sterile organic material, which may be septate or nonseptate and may be present in large or small masses.

(b) PECTINATE BODIES.—These are seen as "broken comb" unilateral projections. This form is characteristic of M. audouini, A. schoenleini and T. gypseum.

(c) RACQUET MYCELIUM (MYCELIUM EN RAQUETTE).— The hyphae show regular enlargement of one end of each segment. They are usually larger than other hyphae. They can usually be seen in any species of Microsporum, in E. inguinale and in T. gypseum.

(d) RESORPTION OF PROTOPLASM.—The protoplasm constituting the contents of the mycelium may be irregularly distributed. This characteristic is emphasized by staining the preparation.

(e) NODULAR ORGAN.—This is an enlargement consisting of closely twisted hyphae. It may be formed by side branches twining around the main stem or by different filaments. This is seen in M. fulvum and in T. gypseum.

(f) FAVIC CHANDELIERS.—These forms, which resemble reindeer horns, are seen only in A. schoenleini and are usually in profusion.

(g) SPIRALS.—Corkscrew-like turns of mycelium are seen particularly in the older fluffy portions of T. gypseum. They are more readily demonstrated on corn meal agar than on dextrose agar.

(h) ARTHROSPORES.—A modification of the hyphae, with thickening of the walls in short segments, these forms may occur singly or in series.

2. REPRODUCTIVE FORMS

Reproduction occurs by asexual spores. These are classed as macroconidia or as microconidia, according to their size.

(a) MACROCONIDIA.

(*1*) *Fuseaux* (*pleuriseptate bundles, spindle spores*).—These are oat-shaped spores which may be connected with mycelium or may be free, since they are readily detached. They may taper at both ends, as in M. lanosum, or one end may be blunt, as in E. inguinale. In some of the Trichophyta they are usually observed while attached to mycelium. As a rule they are septate when fully developed; sometimes the partitions are incomplete, if the specimen is immature. Some workers classify a dermatophyte according to the length of the fuseaux. It is our opinion that, in part at least, the length of the fuseaux may depend on the nutritional content of the medium.

(*2*) *Chlamydospores.*—These large, thick-walled spores are observed along the course of a hypha, at its terminus or on a lateral branch. They may be seen in most old growths, particularly in A. schoenleini or M. albicans, and in the old parts of the colony of E. inguinale. Evidence indicates that chlamydospores are of vegetative function and perhaps should more logically be considered with the preceding group (vegetative forms).

(b) MICROCONIDIA (ALEUROSPORES).—1. The small round or oval spores may be seen free, occurring singly or in grapelike clusters (*grappes*).

2. The small spores may be seen in the substance of the mycelium and are then called arthrospores.

3. If the spores are directly attached to mycelium or to short stocks, the resulting structures may be referred to as hyphae sporiferae (thyrsi sporiferi). Sometimes the mycelium bearing spores in this manner is of smaller caliber than sterile mycelium in the same field or from the same colony.

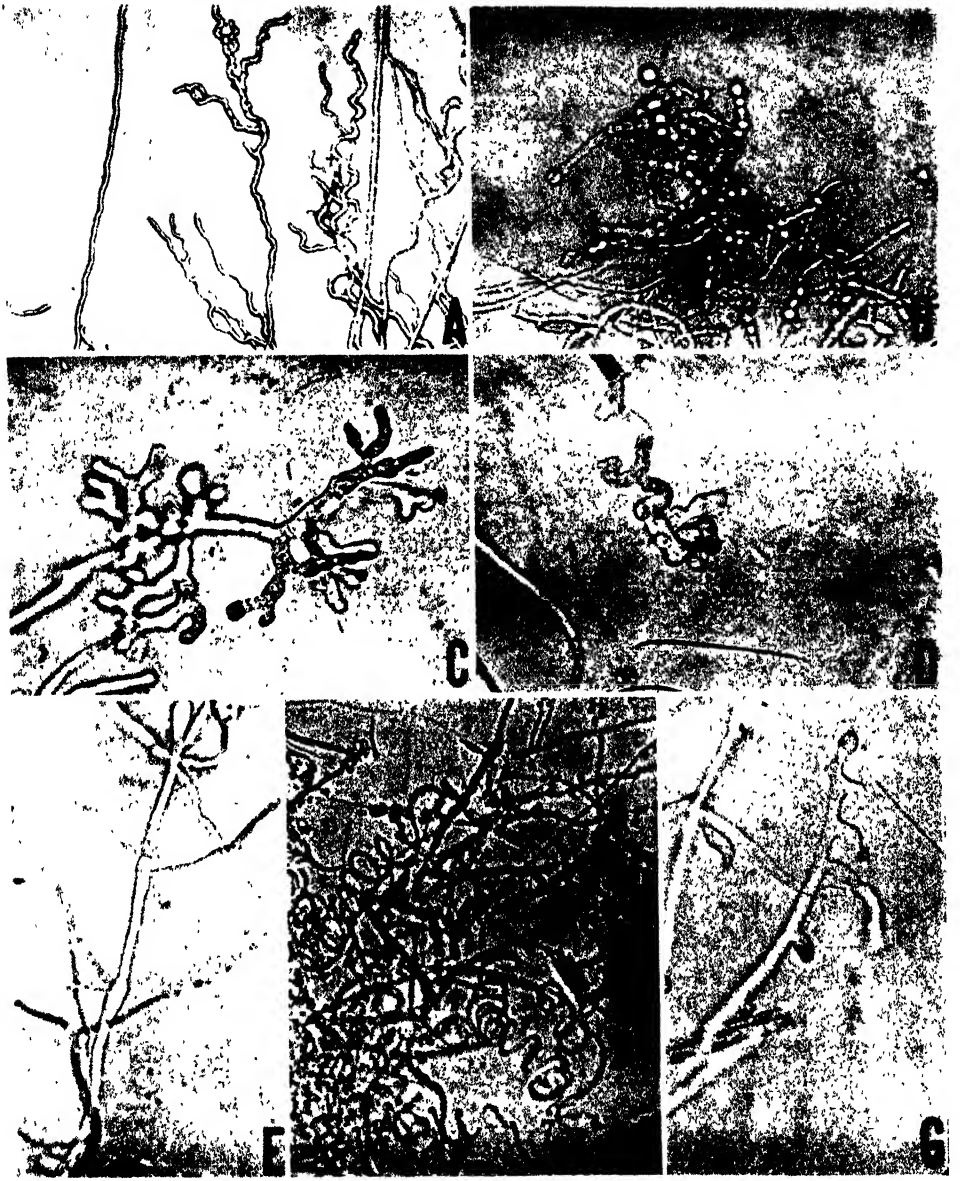

FIG. 74. Common vegetative variations found in the dermatophytes. *A*, simple vegetative filaments; × 175. *B*, chlamydospores; × 175. *C*, favic chandeliers; × 345. *D*, nodular organ; × 640. *E*, racquet mycelium; × 345. *F*, spirals; × 345. *G*, pectinate bodies; × 640.

These spores are the first formed and are to be found in specimens from the peripheral portions of a growth.

3. FEATURES OF DIFFERENT GENERA

The following summary is incomplete, and the various forms listed may not be seen in each species. The outline may be useful for a rapid check.

(a) MICROSPORUM

1. Pectinate bodies (not seen in Epidermophyton, Achorion or Trichophyton, except T. gypseum).
2. Nodular organ, seen in M. fulvum (also in T. gypseum).
3. Racquet mycelium (*mycelium en raquette*).
4. Fuseaux are tapering instead of blunt-ended (E. inguinale) or terminal (T. gypseum). They are few in the human microspora (M. audouini) and more plentiful in M. lanosum.
5. Chlamydospores.
6. Microconidia, usually occurring as hyphae sporiferae.

(b) TRICHOPHYTON

1. Spirals, seen in the T. gypseum group.
2. Nodular organ, in T. gypseum.
3. Chlamydospores.
4. Microconidia (on thyrsi sporiferi and in *grappes*).
5. Arthrospores (in direct mounts and in old cultures).

(c) EPIDERMOPHYTON

1. No spiral hyphae.
2. No pectinate bodies.
3. Racquet mycelium may be noted.
4. Macroconidia (fuseaux), blunt-end. They are divided by septums into four to six cells.
5. Many chlamydospores in the vegetative part of the colony.
6. No spore-bearing hyphae.
7. Arthrospores in profusion.

(d) ACHORION

1. Favic chandeliers (typical).
2. Chlamydospores (numerous).
3. Pectinate bodies.
4. No fuseaux.
5. No nodular organs, racquet mycelium or spirals.
6. Arthrospores.

CHAPTER XXVI

Animal Inoculation

THE inoculation of animals with material from patients for the purpose of diagnosis is seldom resorted to if a superficial infection is suspected. Direct microscopic examination and a cultural study are preferable. For patients with a deep mycosis, a positive diagnosis may be difficult; in such instances the inoculation of animals susceptible to the infection may be advisable. The kind of animal to be used may depend on the infecting micro-organism, since there is variance in susceptibility. Animal inoculation has also been used to determine pathogenicity when a new fungus is isolated or when a fungus which is usually saprophytic is under suspicion. The results must here be interpreted with caution, as differences in susceptibilities of different laboratory animals show that human beings may likewise respond in an individual manner. At times, contaminating bacteria and fungi crowd out the pathogenic growth on the agar slant. If the material is injected into a suitable laboratory animal, the pathogenic fungus may invade susceptible tissues and organs from which it may be cultured in pure form. When a fungus becomes pleomorphic, its original appearance may sometimes be restored by passage through a laboratory animal. Furthermore, the recovery and recognition of characteristic spore forms may be difficult from the cultural growth, whereas such forms may develop in laboratory animals.

Guinea-pigs, rats, mice and rabbits are usually employed. Cats (especially kittens) may be used for cutaneous inoculation. In the first group, inoculations may be cutaneous, intraperitoneal or testicular. The inoculum is usually a saline suspension freshly prepared from the cultural growth on dextrose agar or from finely ground fresh tissue. The animal is examined frequently for evidence of the infection. DeLamater and Benham described the course of the infection in animals successfully inoculated with a ringworm fungus. It is sufficient here to note that the response is confined to the epidermal structures of the animal. When a "take" occurs after inoculation

of a fungus which causes a deep or systemic infection in human beings, a comparable infection is looked for in the experimental animal. If it dies spontaneously, postmortem examination will reveal the extent of the infection and something of its character. If the animal is still living six or eight weeks after the inoculation, it may be killed. According to Weidman, mice and rats are the animals of choice for testing pathogenicity of fungi. Practical advantages in using mice when possible (such as with C. immitis) are the facility of sterilization of the glass jar housing the mice, the ready collection of excreta and the rapid course of the infection.

When difficulty is encountered in establishing a laboratory infection, resistance of the skin may sometimes be lowered by repeated inoculation of infective material into the same site.

For the care of laboratory animals and further details of technic, the reader is referred to the text of Kolmer and Boerner, mentioned in the list of reference books, page 357.

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CHAPTER XXVII

Technic of Passive Transfer Test

WALZER introduced the passive transfer technic to clinical practice. The test is not extensively used in connection with fungous diseases but may be useful when direct testing with trichophytin and other extracts is not feasible.

1. TECHNIC

1. Ten cc. of blood is withdrawn from the patient, using a dry syringe. This blood is transferred to a sterile centrifuge tube.

2. If plasma is desired, glass beads in the tube are shaken and the blood is centrifuged immediately.

3. If serum is desired, the clot is allowed to retract, the material being kept in the ice box. When the clot has retracted the specimen is centrifuged.

4. The serum or plasma is then removed aseptically and stored in the ice box until used. It may be mixed with equal parts of normal saline. Phenol (0.4 per cent) may or may not be added.

5. The patient must be examined and found free from contagious or infectious disease. In particular, a blood test for syphilis should be performed before the serum or plasma is used on another subject.

6. The recipient should be healthy, should not be subject to a major allergy and preferably should not be harboring pathogenic fungi.

7. The serum or plasma is injected intracutaneously into as many sites as there are test substances. If the left side of the back is used for the actual test, the right side in a symmetrical location can be utilized for the control. The sites of injection are then ringed with mercurochrome or some other dye.

8. In 24 to 48 hours, the recipient is ready for the actual testing. The material is injected intracutaneously, suitably diluted, into the exact sites where the serum or plasma was previously introduced. If possible, not only use the same needle puncture but carry the substance into the skin

in an identical direction. At a point on the right side of the back at a symmetrically selected area, an injection is then made for control.

2. INTERPRETATION

The interpretation depends on the development of skin changes at the test site. The reaction is rarely as pronounced as in direct testing. It also evolves more slowly. The degree of reaction is determined by comparison with the control. The test site or sites should be observed after 10 minutes (for an immediate wheal reaction); after 48 hours and one week the presence of a delayed (tuberculin-type) response has not been reported. A positive reaction demonstrates the presence of sensitizing antibodies (reagins) circulating in the patient's blood. A negative reaction does not necessarily mean that the patient is not sensitive to the test substance.

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CHAPTER XXVIII

Testing the Fungistatic and Fungicidal Power of Drugs and Chemicals

WE HAVE previously mentioned that the therapy of the mycoses is not entirely satisfactory. The reason for the efficacy of certain methods of treatment with certain types of mycoses and the lack of effect with other types has not been satisfactorily explained. We believe that biologic processes initiated by the invasion of the skin by some species of fungi determine the response to therapy, the nature of the local treatment in such cases being unimportant so long as the skin is not irritated. When sensitization of the skin is lacking, there is little tendency to spontaneous cure. Finding drugs for the effective treatment of such infections offers a challenge which is engaging the attention of numerous investigators. Since the development of sensitivity of the skin and of immunity is not yet a practical therapeutic procedure, the testing of drugs and chemicals in the hope of finding potent fungicides will continue.

During the past few years particular emphasis has centered on the fatty acids. It has long been known that the acid mantle of the skin has a protective action against bacteria and fungi. Peck and his associates demonstrated that certain fatty acids found in human sweat were effective antifungal agents.

1. TESTING FUNGISTATIC POWER

(a) METHOD OF SCHAMBERG AND KOLMER.—A tube of dextrose agar is melted, and exactly 4 cc. of the agar is placed in a clean tube. The accurately diluted drug is added (in aqueous solution if possible). The pledget of cotton is replaced, the tube is sterilized in the autoclave, and the tube is slanted. The strain of fungus to be tested should be freshly isolated. After the medium has been seeded the tube is incubated at room temperature. A number of dilutions of the drug should be used, and each test

should be repeated in order to insure accuracy. If the drug to be tested is thermolabile, the agar and drug should be sterilized separately and then mixed. The drug may be freed from contamination by ultrafiltration.

(b) BROTH DILUTION METHOD.—Similar to the first method, this procedure utilizes a liquid (broth) medium. Chemicals to be tested show more effective fungicidal power in this medium than when agar is used.

(c) DISK DIFFUSION METHOD.—A series of dilutions is made of the drug to be tested. Filter paper disks of standard size are impregnated with the various dilutions and placed on the agar plate previously seeded by the test organism. An accurate measurement is made of the zone of inhibition.

2. TESTING FUNGICIDAL POWER

(Method of Schamberg and Kolmer; McCrea)

Cultural growths free from agar are shaken with glass beads in sterile saline solution for 10 minutes. The density is determined by comparison with a standard such as tube 5 of the McFarland nephelometer. A solution of the drug to be tested is diluted in distilled water. Equal parts of varying dilutions of the drug and of the suspension of culture are mixed and kept at a temperature of 20 C. Several loopfuls are transferred to slants of dextrose agar at intervals of 15 minutes, one hour, three hours and 24 hours. Control tests should be made, saline solution being used instead of the diluted drug. The results will be apparent within two to three weeks.

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CHAPTER XXIX

Filtered Ultraviolet Radiation (Wood's Light)

THE use of filtered ultraviolet rays is important as an additional method of investigating some mycoses and of determining the causative species of fungus. The "black light" has been the subject of extensive investigation; it is used in many different industries, where substances such as certain minerals show characteristic fluorescent properties. Spurious currency, forged checks and false covers over paintings may be revealed under the filtered rays when the true nature would not be readily detected in daylight. Margarot and Devèze first drew attention to the value of filtered ultraviolet rays as a diagnostic aid in infections of the scalp with Microsporum.

1. SOURCE OF ULTRAVIOLET RAYS

As a rule, it is not practicable to use the sun's rays as a source of ultraviolet rays. However, any of the ordinary office lamps for the production of ultraviolet rays, whether air-cooled or water-cooled, is suitable for this purpose. Less expensive lamps are also serviceable, although the heat generated is a drawback. Davidson and his co-workers have devised two different portable lamps which have proved satisfactory for the detection of tinea capitis. The directions given for their construction, however, are rather vague in certain particulars. Another source of light is a commercial lamp used for indoor photography in which there is an overloaded filament which produces the requisite bright rays but has a correspondingly shorter life than the filament of an ordinary lamp. Although the intensity of optimum rays from its beam is not so great as with the aforementioned lamps, the photographic lamp is nevertheless a satisfactory substitute for the usual ultraviolet lamp.

2. FILTER

The type and thickness of the glass filter through which the ultraviolet rays pass are of great importance. This is especially true when the fluorescent colorations of cultures of fungi are being observed. Divergent results may be obtained by different observers owing to a difference in the type of glass filter or in its thickness. We have found that the wavelengths in the near portion of the ultraviolet part of the spectrum (in the region of 3,650 angstroms) offer optimum fluorescent value. Many different types of glass have been tried; an adequate type is the Corning glass violet ultra, no. 586, polished to a thickness of between 4 and 5 mm. In its molded form it is usually from 7 to 8 mm. thick, and unless the source of light is extremely powerful, not enough ultraviolet rays are transmitted to produce the desired results. The glass is sodium barium silicate containing slightly less than 9 per cent nickel oxide. As the glass is not heat resistant, care must be exercised that overheating does not take place, or cracking will result.

3. EXCLUSION OF UNWANTED RAYS

The room in which the examination is made must be darkened, and in addition most of the visible rays from the ultraviolet lamp must be excluded by a suitable attachment, so that only the rays of light which are not absorbed will pass through the filter. A tinsmith's services may be utilized, or a molded copper attachment may be fitted to the lamp, leaving an open slot for the filter. Mr. Harry Ashmore, an engineer, made a satisfactory attachment of this type for us. When the source of light generates considerable heat, suitable provision must be made for ventilation. Some commercial lamps are now sold with attachments for the exclusion of the unwanted rays.

The unit here described is light, easily attached and detached and readily stored, and it has proved durable in our hands. Any of the better makes of lamp for the production of ultraviolet rays may be used as a source of radiation. The attachment is constructed of 1 sq. yd. of light-proof black rubberized focusing cloth (obtainable at a camera shop). A hole 5 in. (12.5 cm.) square or smaller is cut near the center of the cloth, the size depending on the size of the glass filter. It is suggested that the 5 in. hole be used when the glass filter is 6½ in. (16.5 cm.) square. The edges of the hole are hemmed. Then the glass filter is placed over this hole, overlapping the cloth on each side. Elastic loops are sewed diagonally across the four corners to hold the glass in place. If the fit is snug, no light will seep around

the edge of the glass. Around the edge of the cloth is sewed a hem, in which is placed an elastic drawstring. The cloth is then placed around the hood of an ultraviolet lamp, and the drawstring is tightened until the fit is close enough to exclude visible rays. The ends of the drawstring may then be sewed together, so that later the cloth may be quickly stretched around the hood of the lamp. In order to protect the glass filter from breakage, a wooden frame may be glued to its edges. When lamps that produce considerable heat are used, the cloth may not wear well because of its rubber content. This objection does not arise when a better make of lamp is used. The approximate cost of the attachment (with 6½ in. filter) is $5.50. There have been developed several units in which the filter is in the glass surrounding the filament. Such portable lamps may be purchased from the Westinghouse Electric and Manufacturing Company, Long Island City, N. Y., or from the Strobelite Company, New York City. We have found both types to be satisfactory for our work.

4. USE OF THE RAYS

In dermatologic practice the important fluorescent effects noted when the filtered ultraviolet rays are used as a sole source of radiation may help to detect pathologic conditions and to differentiate fungi in cultures.

1. The value of the rays in cases of tinea capitis cannot be overstressed; they aid not only in establishing a diagnosis but in following the progress of the disease and in determining when cure has taken place. Furthermore, in certain cases of infection with M. audouini when regrowth of hair is considerable, the diagnosis of tinea capitis may not be suspected. In such instances, when only scaling of the scalp may be noted, fluorescence of the affected hairs is characteristic. If the disease is unrecognized, children with this condition constitute a serious menace, as they are potential foci for dissemination to other children.

(a) In all types of infection due to Microsporum, except with M. ferrugineum, the affected hairs appear as luminous, short, yellowish-green stubs.

(b) In infections with Trichophyton endothrix the affected hairs are dull and bluish. This observation is not in agreement with that of Davidson and Gregory, who stated that hairs infected with A. schoenleini fluoresce like those infected with Microsporum and that all the hairs infected with Trichophyton do not fluoresce. It is true that hairs present in follicles invaded by Trichophyton ectothrix do not fluoresce, but in our experience in every case of infection with T. violaceum (endothrix) fluorescence of the infected hairs was a useful observation.

(c) In infections due to Achorion schoenleini the color is greenish but is usually less luminous than in infections due to Microsporum.

2. Animal carriers (particularly kittens) of certain pathogenic fungi may be detected by fluorescence of affected hairs, which when observed under filtered ultraviolet rays have an appearance identical with that of human hairs affected with the disease. (See section on tinea capitis.)

3. Tinea versicolor shows an individualistic color sufficient not only to establish the correct diagnosis but to determine the extent of the eruption, even when it has faded so that its presence cannot be detected clinically. Other fungous eruptions, such as tinea circinata, tinea cruris and dermatophytosis of the feet, and the secondary eczematous and dyshidrotic eruptions of the hands and other parts, as well as infections with Monilia and the deep fungous infections (sporotrichosis, actinomycosis, blastomycosis, coccidioidal granuloma, etc.) do not fluoresce in any characteristic fashion when observed under filtered ultraviolet rays.

4. Hairs affected by lepothrix fluoresce.

5. Keratin fluoresces, and when it is increased more luminosity may be seen. The palm is brighter than the dorsum of the hand. Normal teeth and nails fluoresce brilliantly. The differentiation of certain diseases of the nails is aided. Warts and keratoses show a bright fluorescence, while molluscum bodies exhibit a dark center.

6. Some fading and indistinct eruptions become clearer when observed under filtered ultraviolet rays. An accentuation of the syphilitic roseola is frequently apparent, and this finding is useful when the diagnosis is not easily made, particularly when concomitant findings are not present. Lentiginous and pigmented lesions usually appear darker when seen under filtered ultraviolet rays than when observed in ordinary light.

7. Many inorganic substances fluoresce. When a drug such as salicylic acid or a product such as petrolatum is present on skin examined under filtered ultraviolet rays the underlying condition may be masked.

8. Various fungous growths in culture may be distinguished by their characteristic fluorescent colorations. These will be taken up in detail when the different fungi are considered.

It may be mentioned here that we have studied this method of determination of species of fungi for many years and can testify to its value and specificity. The characteristic fluorescence of a fungus appears to be its most stable feature, resisting so-called pleomorphic changes. Variants of a species which may appear totally unlike are recognized to be related by means of the appearance under the rays. It seems to us that the method has been in use sufficiently long to prove of merit and should be more widely employed.

That fungi in culture fluoresce was first noted by Margarot and Devèze. Vigne mentioned that T. crateriforme shows a strong violet fluorescence in culture. Bommer pointed out that fungi in culture display a fluorescence different from that observed in the diseased hair, and cited as an example the fact that whereas hairs infected with M. audouini have a green fluorescence, the culture shows a yellowish-brown tint with a light violet shimmer on the surface. He stated that in an examination of about 200 cultures of fungi on Sabouraud's medium he could not establish a variance in fluorescence corresponding to the cultural differences. Using a special medium containing urea and sucrose with the addition of minerals, the reaction of which was neutral, Mallinckrodt-Haupt and Carrié obtained differences in fluorescence among several different species of fungi. Microsporum audouini showed a yellowish-green fluorescence and T. gypseum-asteroides a greenish fluorescence, which later became blue. Epidermophyton inguinale and Cryptococcus showed weak or no fluorescence. Achorion schoenleini was at first greenish; in a month and a half it was copper-blue. Sporotrichum beurmanni exhibited a green fluorescence, subsequently becoming blue. The investigators were unable to isolate chemically and to crystallize out the substance causing the fluorescence. Experimental studies indicated, however, that the color of the fluorescence depends on the reaction. The addition of alkali to a culture filtrate caused a greenish fluorescence, while the addition of hydrochloric acid caused a bluish fluorescence. It is interesting here to note that Cortese, in working with several species of Actinomycetes, was able to extract fluorescent material with weak alcohol, purifying it by shaking with acidified ether. The substance was found to be amorphous, odorless and reddish brown. It belonged to the group of porphyrins and showed a marked fluorescence in high dilutions. It is of interest that the character of the culture mediums, in our experience, has little effect on the fluorescent colorations of fungi.

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CHAPTER XXX

The Trichophytin Test: Technical Details

IF UNIFORM results are to be obtained from the test, a number of details must be carefully considered and the exact technic should be mastered. The test is perhaps as difficult to perform as an accurate white blood cell and differential count. The main technical considerations are as follows:

1. The syringe and needle should be freshly sterilized.

2. The vaccine should be free from contamination. The addition of 0.5 per cent phenol to the test solution is a practical way of assuring sterility. Boiling a solution of trichophytin does not appear to affect its potency. Reactions to ordinary trichophytin and to trichophytin heated two hours in a steam bath were identical.

3. The concentration of the trichophytin should be as low as possible while still capable of eliciting reactions in sensitive persons, such as Metz 1:100 or Lederle 1:30.

4. As a rule the use of one of several commercial extracts is preferable to the use of a homemade product, which is difficult to standardize. It has been noted that a person sensitive to an extract made from one species of Trichophyton usually reacts to an extract made from another species.

5. The vaccine should be carefully introduced intracutaneously. Exactly 0.1 cc. of the test material should be given.

6. Observation of the patient for the presence of a reaction should be made after 10 or 15 minutes (for an immediate wheal reaction), after 48 hours (for the usual eczematous response) and again at the end of one week (for sustained and delayed reactions).

7. The degree of reaction should be judged not by estimation but by measurement, with a rule, of the diameter of the area of skin affected. We found it difficult to set a standard for the immediate wheal responses. The

chief reason for this is the variability of the initial response to the injection of any vaccine in different persons. It appears necessary with each patient to use a control injection of broth, in order to establish a base line. An immediate wheal reaction is indicated by a rapid increase in the size of the elevation over that normally present after any intracutaneous injection and by an irregular border, or pseudopods. Itching may or may not be present. When the diameter is below 1.5 cm. 10 minutes after the injection, the reaction is designated as 1 plus. If the diameter is over 1.5 cm. the reaction is designated as 2 plus, and over 2 cm., 3 plus. After 48 hours and after one week the results of the tests are indicated by a cipher for a negative reaction; a plus-minus sign for an area of slight erythema approximately 0.5 cm. in diameter; 1 plus for 0.5 to 1 cm.; 2 plus for 1 to 1:5 cm.; 3 plus for 1.5 to 2 cm., and 4 plus for an elevated area of reaction 2 cm. or more in diameter.

CHAPTER XXXI

Other Specific Skin Tests

1. THE OIDIOMYCIN TEST

THE precautions described for the use of trichophytin are similar when oidiomycin is used. The commercial vaccine (Lederle) should be diluted in the ratio of 1:150 with sterile saline solution; 0.1 cc. of the extract is the test dose. In interpreting the quantitative reaction of the skin to oidiomycin we read the test as for trichophytin as follows: a cipher indicates a negative reaction; a plus-minus sign an area of slight erythema approximately 0.5 cm. in diameter; 1 plus, 0.5 to 1 cm.; 2 plus, 1 to 1.5 cm.; 3 plus, 1.5 to 2 cm., and 4 plus, an elevated area of reaction 2 cm. or more in diameter. The strongest reactions are those which remain for a week or more. We have occasionally observed an immediate wheal reaction to oidiomycin.

2. THE COCCIDIOIDIN TEST

The vaccine is prepared from the growth on Bureau of Animal Industry Synthetic Media after two months at 37 C. A dilution is made of 1:1,000 normal saline to which is added merthiolate. The material should be passed through a Berkefeld filter and tested for sterility.

3. THE BLASTOMYCIN TEST

The antigen is made by heat-killing the yeastlike growth obtained by culturing B. dermatitidis at 37 C. A dilution of 1:1,000 is made with sterile saline. The test dose is 0.1 cc.

4. THE SPOROTRICHIN TEST

The vaccine is made in a manner similar to trichophytin. According to du Toit, the colony should be killed by heat and diluted with saline solution.

CHAPTER XXXII

Characteristics of Pathogenic Fungi

THE list of fungi which follows includes those which seem to be most important from the practical standpoint. It is by no means complete. Davidson and Gregory stated that at least 180 species of dermatophytes have been mentioned in the literature as pathogenic for man. The majority of these species have been isolated only once or only a few times, so they may safely be ignored. In other parts of the United States and in foreign countries the flora may vary somewhat, and some micro-organisms which we rarely see in New York may elsewhere be of more common occurrence.

Brief data on the clinical aspects and sensitization phenomena of the species of fungi are included with the descriptions of their microscopic and cultural characteristics. Further clinical information is available in Part One, where the various mycoses which they cause are described.

The following fungi will be described in detail:

1. Microsporum audouini
2. Microsporum lanosum
3. Microsporum fulvum
4. Microsporum ferrugineum
5. Achorion schoenleini
6. Trichophyton alba (faviforme)
7. Trichophyton violaceum
8. Trichophyton crateriforme
9. Trichophyton sulfureum
10. Trichophyton gypseum
11. Trichophyton purpureum
12. Epidermophyton inguinale
13. Monilia albicans
14. Malassezia furfur
15. Actinomyces minutissimus
16. Endodermophyton tropicale

17. Hormodendrum pedrosoi
18. Hormodendrum compactum
19. Phialophora verrucosa
20. Actinomyces bovis
21. Sporotrichum schencki
22. Blastomyces dermatitidis
23. Histoplasma capsulatum
24. Coccidioides immitis
25. Paracoccidioides brasiliensis
26. Torula histolytica
27. Rhinosporidium seeberi

It is of interest that these fungi are rarely found on the normal skin or its appendages. The studies of Hopkins and Benham, of Burgess, of Stumpf and of Downing and his co-workers point to the fact that the flora of the skin contains many filamentous and yeastlike fungi but that these are almost always saprophytes. Our observations are in agreement with the conclusions of these workers. In the series of 100 patients studied by Downing, Nye and Cousins, material from three different sites on each patient was cultured. In only two of 300 specimens were pathogenic fungi demonstrated. Burgess reported that in cultural studies of 100 patients he failed to find a single pathogen on normal skin. Cornbleet obtained scrapings from the webs between the fourth and fifth toes of 100 young adults apparently free from tinea pedis. In three instances pathogenic fungi were recovered: E. inguinale twice and M. audouini once. From his repeated failure to find them on the hands and feet of 50 normal persons, Stumpf concluded that pathogenic fungi do not live there as saprophytes.

The isolation of one of these pathogenic micro-organisms from significant pathologic tissue serves as conclusive evidence of the cause of the disease without the necessity of further proof.

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1. MICROSPORUM AUDOUINI

This fungus may be termed the classic cause of ringworm of the scalp. It is endemic in many countries, being chiefly found in the larger cities. Epidemics of tinea capitis in schools, foundling homes and other institutions are usually caused by this fungus. It is the cause in approximately 40 per cent of cases of ringworm of the scalp seen in dispensaries in New York.

(a) CLINICAL CHARACTERISTICS.—As a rule there is little inflammatory reaction in the scalp. Several patches of apparent alopecia are usually noted which, on close inspection, are seen to contain broken-off, stubby hairs. This is the so-called "gray patch" ringworm. The stubs may be colorless and may be extracted with very slight traction. Besides the larger areas, smaller areas, in which only a few hairs are involved, are frequently detected in routine examinations under filtered ultraviolet rays. Occasionally there is an inflammatory reaction in the scalp. Pustulation is uncommon and kerion formation rare, although it has been noted. Ringed, slightly inflamed lesions may be present on the smooth skin, particularly if the patient also has tinea capitis. Other parts of the body, such as the hands, feet and nails, are not affected.

(b) IMMUNOLOGIC REACTIONS.—Occasionally children with infection due to M. audouini have moderate reactions to the intracutaneous test dose of trichophytin. More frequently the reaction is slight or absent; in only a few instances have we observed strong reactions.

(c) MICROSCOPIC FEATURES.—The fungus appears in the form of a mosaic sheath around stubby hairs. There is little tendency to chain formation. The individual elements, or spores, are round and small. In infections of the glabrous skin, mycelium may be detected. Lanugo hairs may occasionally be infected.

(d) CULTURAL CHARACTERISTICS.—Beginning as a white feathery fluff, the colony grows moderately into a grayish-white fluffy culture. The aerial growth is scanty. There is usually a central elevation. Radial grooving may appear, especially on Petri dishes, but this is not constantly or even frequently found on dextrose agar. On maltose agar the formation of radial grooves is one of the chief characteristics. Secondary radial grooves may also form. Pleomorphism is uncommon.

(e) CULTURE MOUNT.—Fuseaux are only occasionally found. Microconidia are present in limited numbers. Chlamydospores and pectinate bodies are frequent; they are more readily observed when corn meal agar is used.

(f) FILTERED ULTRAVIOLET RAYS.—The short, stubby hairs found in the patches of tinea capitis fluoresce as bright, clear green dots. All the hairs in a lesion are usually seen to be involved. The cultural growth in 10 days is dull, clear and mouse-gray throughout.

(g) ANIMAL INOCULATION.—Animals are resistant to infection with this fungus.

(h) DIFFERENTIAL DIAGNOSIS.—The direct examination of an infected hair will show Microsporum if it is present, since the spores are small, occur in large numbers and have a mosaic arrangement outside the hair shaft. On culture M. audouini may be differentiated from M. lanosum because M.

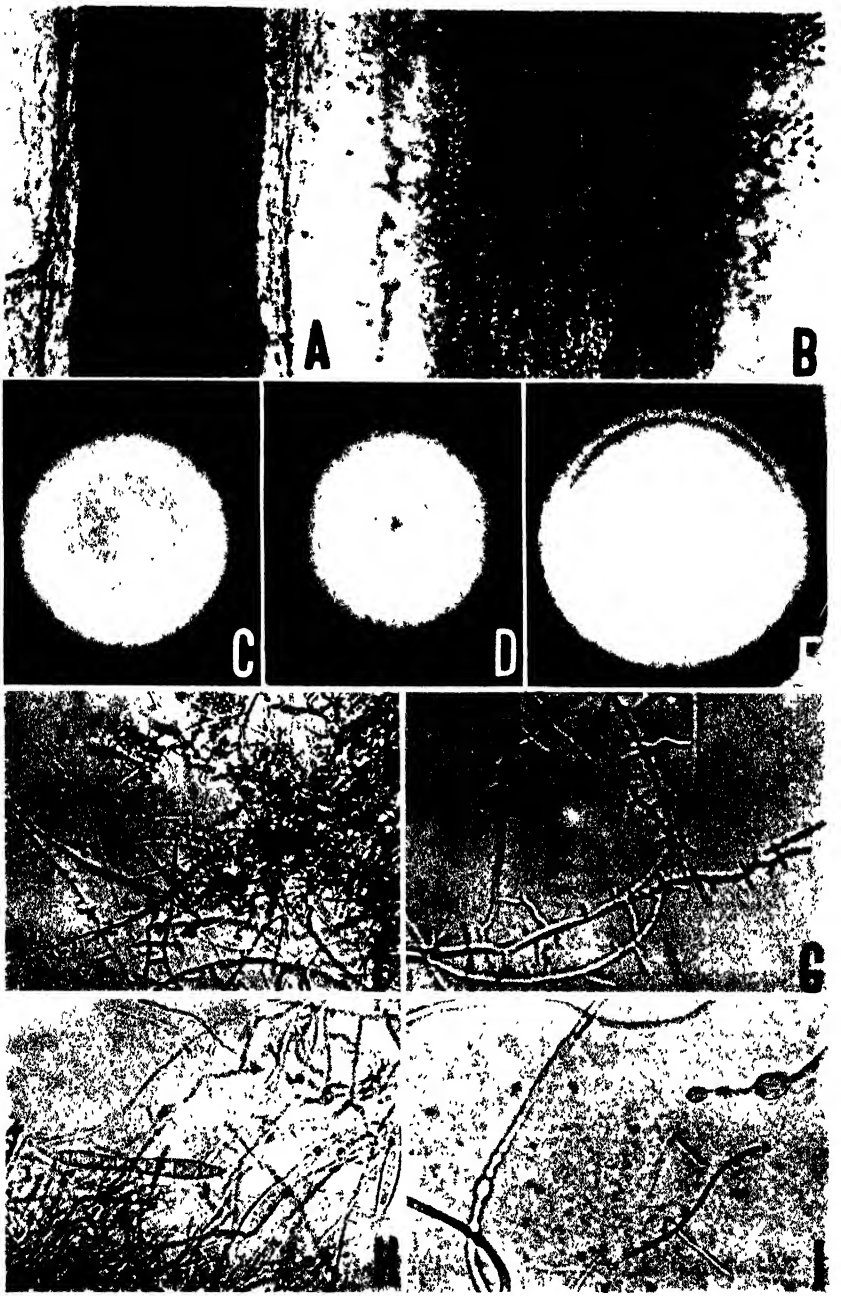

FIG. 75. Microsporum audouini. *A* and *B*, infected hairs, showing mantle of spores; × 175 and × 365, respectively. *C*, *D* and *E*, cultural growths after 10 days, two weeks and six weeks, respectively. *F*, culture mount showing microconidia in clusters and as hyphae sporiferae; ×180. *G*, hyphae sporiferae; × 500. *H*, culture mount from an old culture, showing fuseaux (infrequently observed); × 180. *I*, chlamydospores in vegetative filaments; × 365.

audouini begins to grow later, the young colony is white rather than yellow and the appearance under filtered ultraviolet rays is dull and mouse-gray rather than bright blue and pink. In the culture mount, fuseaux are rarely found, whereas in the culture of M. lanosum fuseaux are normally present in large numbers.

2. MICROSPORUM LANOSUM

This fungus is occasionally seen in Europe. In the United States it is responsible for tinea capitis in about 40 per cent of the cases observed in large Eastern cities and causes the majority of ringworm infections of the scalp in the Southern and Pacific Coast regions.

(a) CLINICAL CHARACTERISTICS.—At times the appearance of the patches of the scalp is indistinguishable from the manifestations of M. audouini. Usually, however, there is at least some erythema, and pustulation of mild or of severe degree may be noted. Kerion is present in one of every 30 cases. The history of infection is short (a few weeks or several months). Occasionally infection may be traced to an animal; pets (kittens and puppies) are sometimes incriminated.

Infections on the smooth skin are also of common occurrence; they are more frequent in children but are occasionally found in adults also. The lesions are usually circinate, with a clearing center and a vesicular border. Infrequently, widespread infections of the glabrous skin occur. The adult beard is also known to have been affected, although not in our experience.

(b) IMMUNOLOGIC REACTIONS.—There is usually a moderate or vigorous reaction to the intracutaneous trichophytin test. In rare instances the reaction is not present.

(c) MICROSCOPIC FEATURES.—The appearance in the sheath around the infected hair is indistinguishable from that of M. audouini in the same location. The individual spores are small and round and are present in clusters. On the smooth skin, mycelium is noted in sparse amounts. Lanugo hair is sometimes affected.

(d) CULTURAL CHARACTERISTICS.—Growth is moderately fast. A downy fluff appears, around which is yellowish pigment. In two weeks the central part of the colony is depressed. The aerial growth is abundant and wooly. The color is a buff-tan. Grooves, if present, are often concentric, although radial grooves are common. Pleomorphism starts with regularity after four or five weeks. Considerable pigment of yellowish color is usually produced in the subsurface portion of the colony.

(e) CULTURE MOUNT.—The characteristic feature is the large number of fuseaux of the tapering variety (taken from the center of the growth). Their

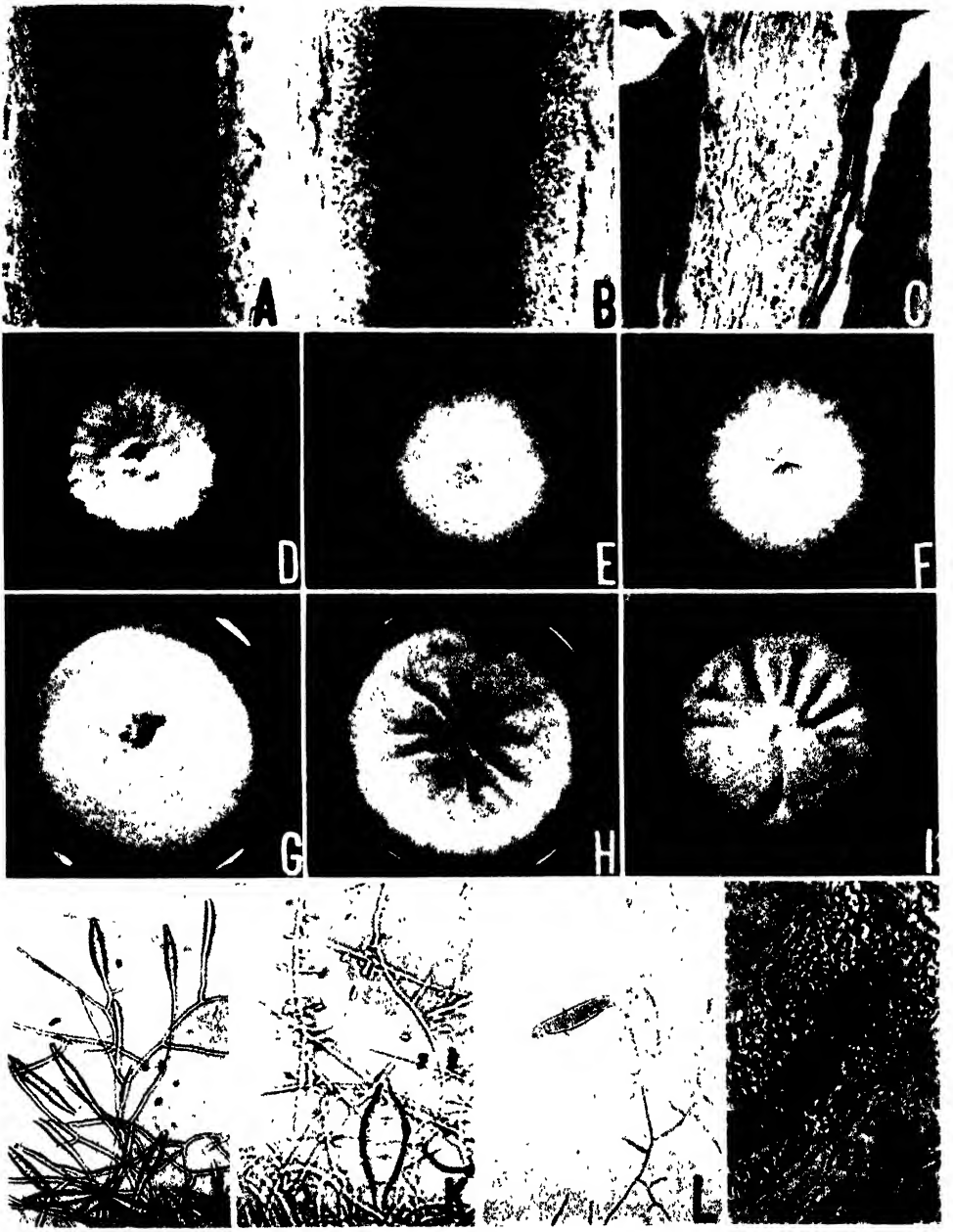

FIG. 76. Microsporum lanosum. *A* and *B*, infected hairs, showing mosaic of spores outside the hair shaft; × 170 and × 350, respectively. *C*, section of cat's skin, showing spores in a follicle. *D*, *E* and *F*, growths on dextrose agar after 10 days. *G*, *H* and *I*, cultural growths after three weeks. Different strains often show minor variations in texture and configuration. *J*, culture mount showing pointed fuseaux; × 75. *K*, microconidia and fuseaux, showing their multicellular character; × 350. *L*, germinating spore; × 175. *M*, infected lanugo hair from a circinate lesion on the arm; × 340.

walls are thick and roughened. There are from four to seven compartments. Microconidia and occasionally racquet mycelium and pectinate bodies may be noted.

(f) FILTERED ULTRAVIOLET RAYS.—The infected hairs, whether on the scalp or extracted, resemble those infected with M. audouini and are a bright, clear green. Within an infected patch, clear areas devoid of hair are often seen. Colonies of M. lanosum after 10 days are also bright and clear. The center of the growth may be lavender-blue, shell-pink or flesh-ocher; the midzone (not always present) is lavender-blue; the edge is olive-drab or mouse-gray.

(g) ANIMAL INOCULATION.—Kittens and puppies as well as laboratory animals are readily infected. Because of this the organism is known as an "animal" Microsporum.

(h) DIFFERENTIAL DIAGNOSIS.—This is discussed in the section on diagnosis of M. audouini, pages 284 and 286.

3. MICROSPORUM FULVUM (MICROSPORUM GYPSEUM; ACHORION GYPSEUM)

Apparently imported from South America, this fungus is occasionally seen in New York. There are few reports of its occurrence elsewhere in the United States. It is another example of an animal Microsporum and has been called the cause of dog favus. Lesions caused by M. fulvum are usually confined to the scalp and glabrous skin, and the patients are almost always children.

(a) CLINICAL CHARACTERISTICS.—In the patients with infections of the scalp which we have studied, a uniformly and severely inflamed patch was noted. The scalp was hypersensitive, and the area of infection was edematous and often kerionic. The prognosis for early cure is good. Treatment should be conservative. On the glabrous skin, ringed lesions of dull red with a clearing center and a vesicular border may be noted. As a rule scaling is scanty.

(b) IMMUNOLOGIC REACTIONS.—Intracutaneous trichophytin tests invariably elicit sizable reactions in patients with infections due to this fungus. This is not surprising in view of the character of the lesions.

(c) MICROSCOPIC FEATURES.—Hairs infected with this organism may show a sheath of spores arranged in rosaries, probably representing the early stage of invasion, and also spores with no linear arrangement. The resemblance to an infection due to A. schoenleini is sometimes striking. When the invasive stage of the infection is over, the appearance of the fungi in fresh preparations is indistinguishable from that of other Micro-

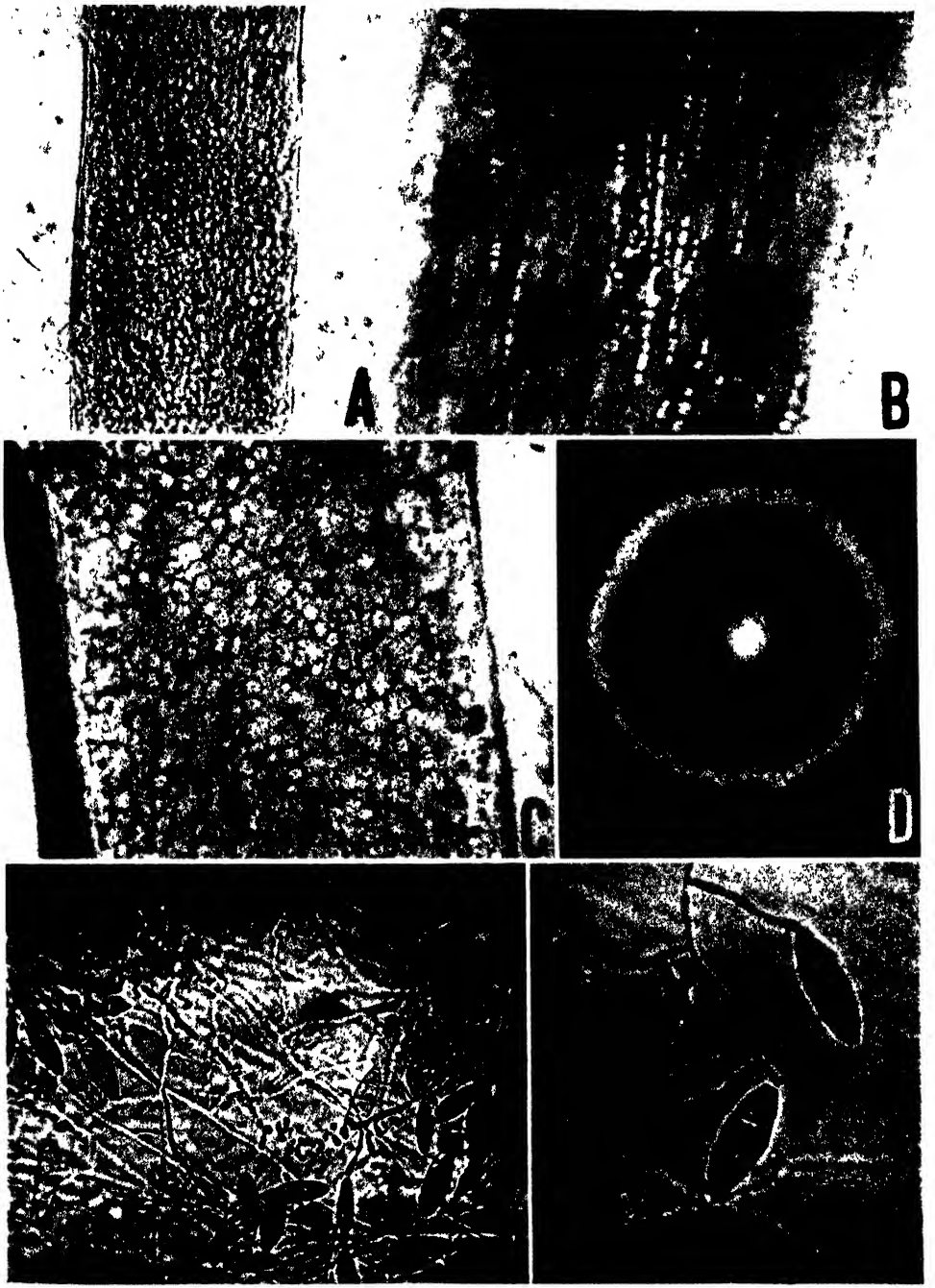

FIG. 77. Microsporum fulvum. *A*, *B* and *C*, infected hairs, showing small spores with a tendency to linear formation. Magnification: *A*, × 220, *B* and *C*, × 435. *D*, the colony after 10 days. *E*, slide culture, showing fuseaux and microconidia; × 220. *F*, typical short rounded fuseaux; × 435.

spora. The hair shaft is not invaded. The fungi in lesions of the smooth skin are noted as short chains of spores; usually the amount of fungous material is scanty.

(d) CULTURAL CHARACTERISTICS.—Few fungi in culture are more easily recognized. The rate of growth is moderately active, and in two weeks there is a central umbo, which may be white, surrounded by a flat, felty growth resembling suede. The cinnamon-brown color of the entire colony is characteristic. If any furrows are present, they are usually concentric rather than radial. The growth continues in an agar slant until the medium is entirely covered. The margin of the colony is usually abrupt. Pleomorphic changes readily occur and are evidenced by the appearance of white tufts on the surface of the colony.

(e) CULTURE MOUNT.—Numerous fuseaux are present. The walls are moderately thick, and the ends are rounded. Racquet mycelium and nodular organs may be found. Small round spores are to be seen in moderate numbers.

(f) FILTERED ULTRAVIOLET RAYS.—When observed in this light, infected hairs fluoresce as light green stubs characteristic of all Microsporum infections. The fluorescence of the hairs may not be noted in an edematous patch; in this case the diseased hairs may be below the surface. The cultural growth is dull, clear and cinnamon-brown throughout.

(g) ANIMAL INOCULATION.—This organism may be transferred to the young of several species of animals.

(h) DIFFERENTIAL DIAGNOSIS.—The microscopic picture may simulate that of the other Microspora, but if the infected hair has been recently invaded, short filaments in the hair shaft may suggest infection with A. schoenleini. The cultural growth is highly characteristic. The fuseaux are of slightly different character and more numerous than with M. lanosum. Nodular organs are not seen in other Microspora.

4. MICROSPORUM FERRUGINEUM

We have isolated this fungus only once. The patient, a Chinese child born in Hawaii, had tinea capitis with little inflammation, the alopecia spreading in concentric rings and progressively. We are unable to find the child after one visit, so the response to therapy is unknown. According to Frederick Reiss, the micro-organism is a common cause of tinea capitis in China. We have received one specimen from American Samoa, where it may be a frequent pathogen.

(a) MICROSCOPIC FEATURES.—The sheath of the invaded hair shows slender filaments (about 3 microns in diameter) packed tightly together

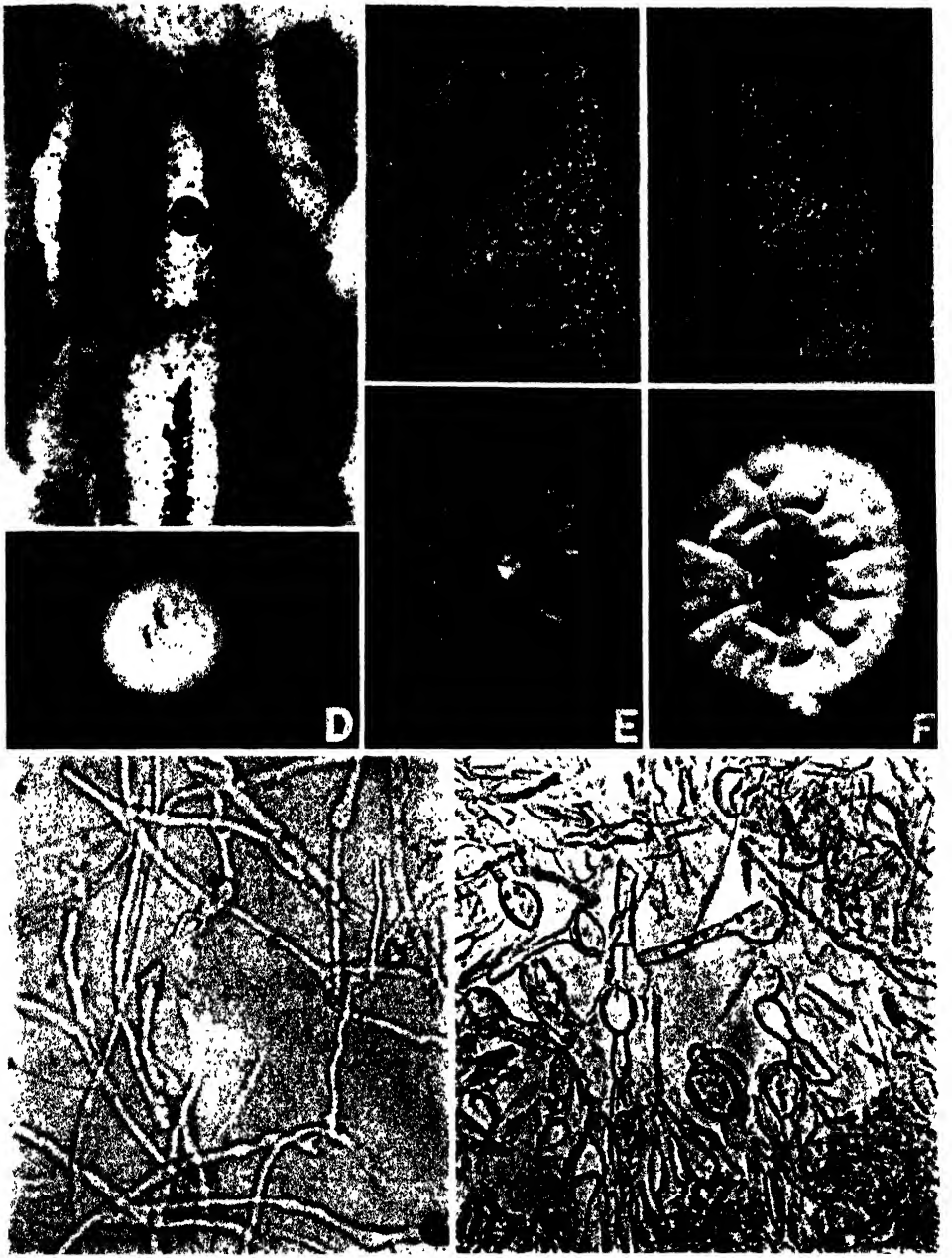

FIG. 78. Microsporum ferrugineum. *A, B* and *C*, infected hair mounted in hydroxide; × 36, × 150 and × 150, respectively. *D, E* and *F*, cultural growth at two weeks, three weeks and four weeks on dextrose agar. *G*, aerial growth of colony is composed of vegetative filaments and a few chlamydospores; × 480. *H*, mount from the substrate of the colony shows large numbers of chlamydospores; × 480. (*Specimen, courtesy of Robert C. Lofgren.*)

and intertwined. At the level of the surface of the scalp, some spores may be found. Presence in scales has not been observed.

(b) CULTURAL CHARACTERISTICS.—Growth is slow. Initially, after isolation, the colony is compact and golden yellow. Some strains have a reddish tone (Plate II, facing p. 227). The center becomes elevated. Irregular convolutions and radial grooves extend to the edge. The edge of the colony is depressed in a narrow band beneath the surface of the agar. The elevated central portion is glabrous, and the remainder of the colony except the narrow edge is downy white.

(c) CULTURE MOUNT.—There is a paucity of spores. Aleurospores are few and atypical. Both terminal and intercalary chlamydospores are present. There are some racquet cells and occasional rudimentary pectinate bodies. The bulk of the mycelium is composed of closely intertwined, irregularly sized filaments with many protuberances.

(d) FILTERED ULTRAVIOLET RAYS.—The infected hairs do not fluoresce. The cultural growth at one month in dextrose agar shows a light yellowish tan. The submerged periphery shows a bright cream color.

(e) ANIMAL INOCULATION.—No laboratory animal is susceptible.

(f) DIFFERENTIAL DIAGNOSIS.—A fungous infection caused by this microorganism should be suspected when the patient comes from the Orient. The infection may be widespread. The tendency to hair destruction down to the surface of the scalp may cause confusion with alopecia areata. The lack of fluorescence of the hairs, the cultural appearance, the fluorescent characteristics of the colony and the lack of spindle spores in the culture mount suffice to differentiate it from other Microspora.

5. ACHORION (TRICHOPHYTON) SCHOENLEINI

This fungus, the cause of favus, is of widespread occurrence, being common in Russia and other European and Asiatic countries. It was formerly prevalent in Scotland and France but is less so now. In the United States it has been isolated mainly in immigrants or their families. There are several areas, however, where favus is endemic.

(a) CLINICAL CHARACTERISTICS.—The scalp, the nails and the smooth skin may be affected. In the scalp, typical scutula may be observed, a thick diffuse crusting may be present, or seborrhea-like scaling alone may develop. The alopecia is patchy, and long hairs may usually be observed in the areas of infection. Scarring and permanent alopecia are the sequelae. On the smooth skin, scutula may develop, or vesicular lesions (favus herpeticus) or scaly dull red plaques may be observed. Infection of the nails may be indistinguishable from onychomycosis due to other fungi.

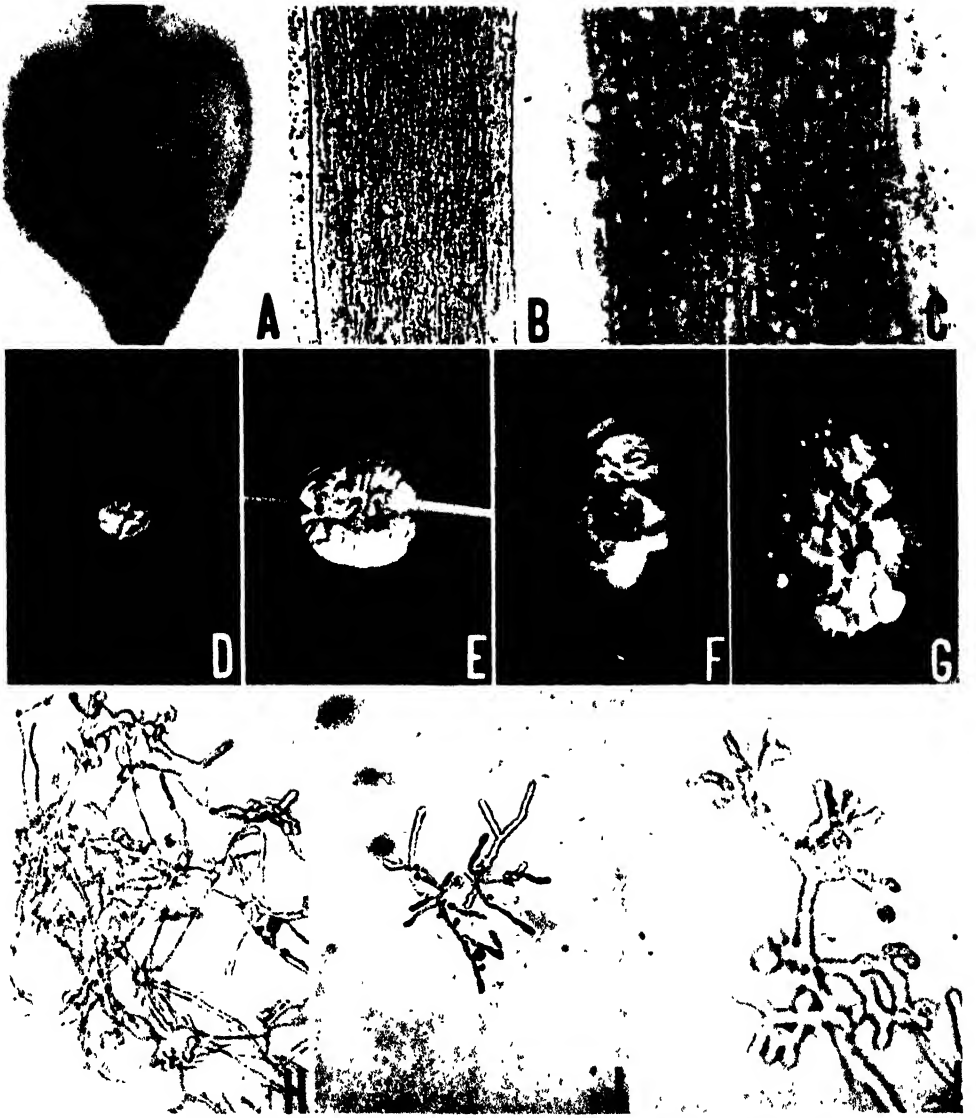

FIG. 79. Achorion schoenleini. *A*, hair surrounded by scutulum composed of filaments and spores; × 35. *B* and *C*, irregular filaments and spores in the hair shaft accompanied by air bubbles; × 165 and × 325, respectively. *D*, colony after two weeks. *E*, colony after one month. *F* and *G*, older growths, showing variations in the texture. *H* and *I*, culture mounts, showing irregularity of form in culture; × 70 and × 165, respectively. *J*, favic chandeliers; × 325.

(b) IMMUNOLOGIC REACTIONS.—A large majority of patients with favus give negative reactions to the intracutaneous test with trichophytin. Occasionally a mild response may be noted.

(c) MICROSCOPIC FEATURES.—Large spores in chains may be found within the hair substance. Air spaces may also be noted in the hair, and air bubbles may be attached to it; this should always direct suspicion toward this organism. If a scutulum is examined, a mass of sporulated hyphae will be found. Material from the superficial lesions of the smooth skin reveals a sparse number of hyphae. The findings in material from infected nails resemble those of other organisms, i.e., chains of spores.

(d) CULTURAL CHARACTERISTICS.—The rate of growth is slow; sometimes three weeks elapse before the primary colony has developed sufficiently to be recognized. The growth is compact and smooth and presents a characteristic waxy appearance. The surface is markedly uneven. Pleomorphism is uncommon. The colony grows down into the medium and in time produces cracking of the agar.

(e) CULTURE MOUNT.—Favic chandeliers are noted; they are diagnostic. Chlamydospores in large numbers may also be observed.

(f) FILTERED ULTRAVIOLET RAYS.—Infected hairs show a greenish fluorescence but are less luminous than hairs infected with Microsporum. The cultural growths have a dull clear olive-gray appearance throughout.

(g) ANIMAL INOCULATION.—Guinea-pigs may be infected. The organism is also inoculable into rats, mice, cats and rabbits (Dodge).

(h) DIFFERENTIAL DIAGNOSIS.—The infected hairs are not always short. The appearance of a direct mount reveals an endothrix infection. The number of filaments is less than with other organisms; the presence of air bubbles is also highly suggestive, and the irregular segmentation of the filaments is characteristic. On culture, little difficulty is experienced in differentiating other growths. The favic chandeliers visible in a culture mount are seen in no other cultural growth.

6. TRICHOPHYTON ALBA (FAVIFORME)

An uncommon isolate, the usual clinical response is an intensely inflamed, boggy, rapidly spreading eruption of the smooth skin. A history of contact with infected animals may be significant.

(a) IMMUNE REACTIONS.—The trichophytin test elicits strong reactions.

(b) MICROSCOPIC FEATURES.—Masses of large spores in filaments may be observed.

(c) CULTURAL CHARACTERISTICS.—The growth is slow. Small yellow glabrous or waxy colonies, mostly subsurface, gradually form some areas of

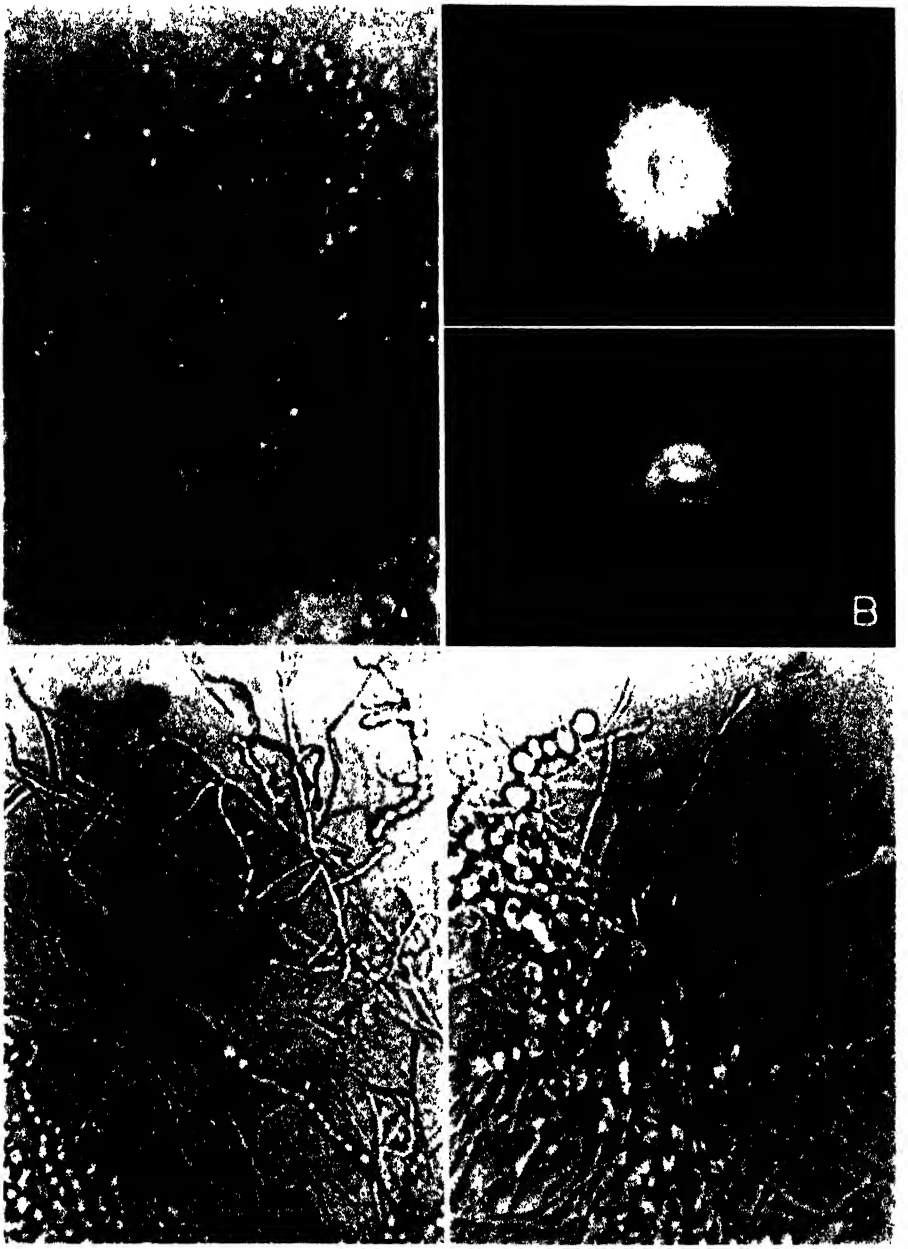

FIG. 80. Trichophyton alba (faviforme). *A*, direct mount, showing spores in chains; × 480. *B*, growths on dextrose agar after six weeks. *C* and *D*, culture mounts, revealing simple filaments and large numbers of chlamydospores, but no evidence of conidia or chandeliers; × 220 and × 480.

velvety surface with a pattern of irregular radial folds and elevations.

(d) CULTURE MOUNT.—Vegetative elements are simple, delicate and undifferentiated. Chlamydospores are numerous. No free spores, fuseaux or chandeliers are present.

(e) FILTERED ULTRAVIOLET RAYS.—A soft, pinkish-lilac color develops.

(f) ANIMAL INOCULATION.—Infection is difficult to reproduce in laboratory animals.

(g) DIFFERENTIAL DIAGNOSIS.—The colonies of this organism and of Achorion schoenleini may be similar. The velvety surface and regular pattern of grooves are usually distinct. The absence of chandeliers is suggestive.

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7. TRICHOPHYTON VIOLACEUM

This organism is widely distributed throughout the world, being a common cause of infections of the scalp, beard and nails in Russia, Poland and Italy as well as other European countries and states in the Near East. It is not unknown in Australia. In the United States, the organism is chiefly found in immigrants or their siblings, but sporadic cases have been noted in native stock.

(a) CLINICAL CHARACTERISTICS.—Infections caused by this fungus are usually insidious in their development and exceedingly refractory to treatment. On the scalp, the hairs are attacked and break off close to the skin. Small pustules and follicular crusts usually form. Permanent scarring may result. Similar mildly inflammatory lesions may appear on the bearded region. When the infection spreads to the nails, rarely more than one or two become affected. The nails are crumbly, yellowish and opaque. In this location the fungus may be difficult to demonstrate.

(b) IMMUNOLOGIC REACTIONS.—Negative or very slight reactions are noted after the intracutaneous trichophytin test.

(c) MICROSCOPIC FEATURES.—This organism is an endothrix Trichophyton, invading the hair shaft. The spores are larger than those of the Microspora and are arranged in rows or beads. No fungi are found on the surfaces of the hairs. In scales or nail tissue, the organism is also observed in the form of sporulated mycelium.

(d) CULTURAL CHARACTERISTICS.—The rate of growth is slow; at prime the colony is small and well defined. It is smooth, shiny, compact and almost yeastlike, with a typical deep violet color. The surface shows convolutions,

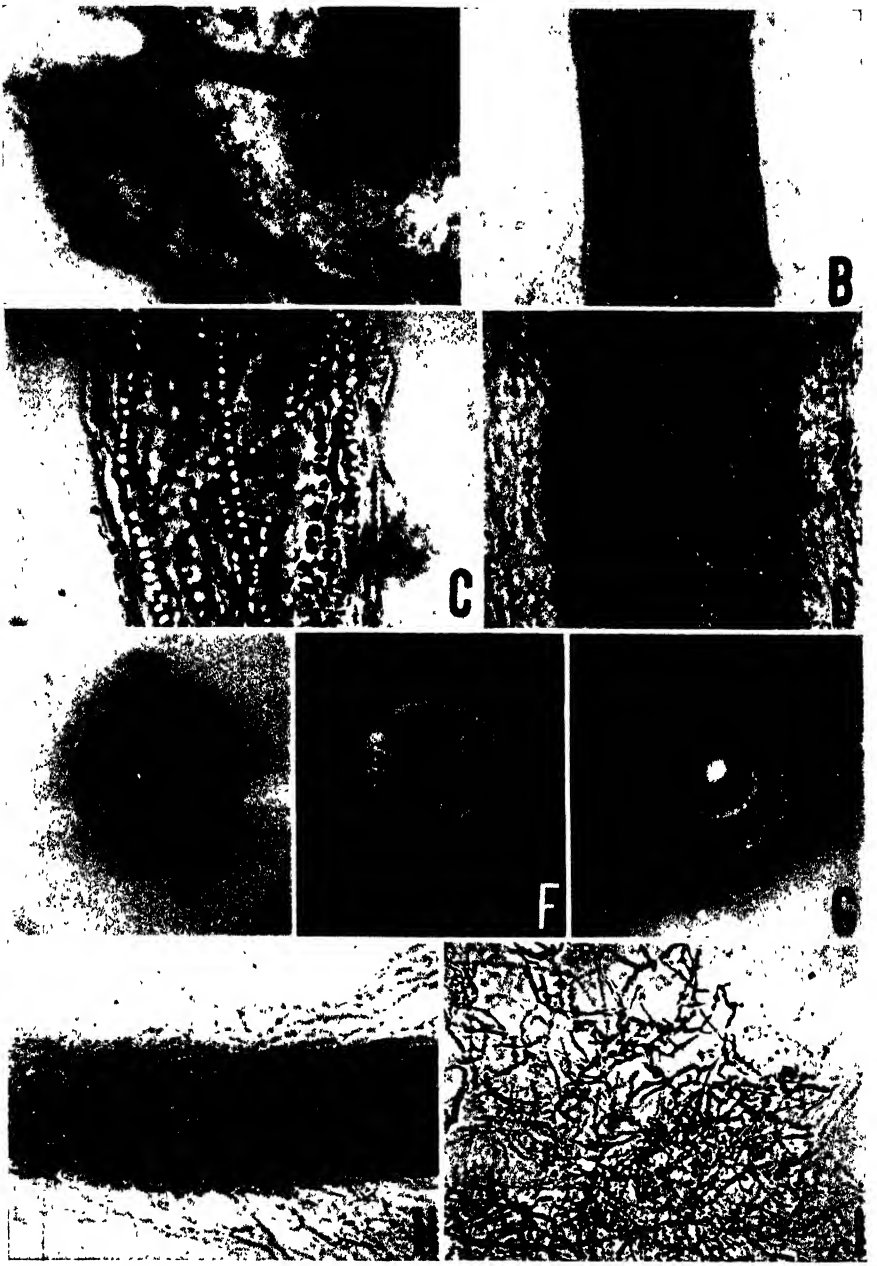

FIG. 81. Trichophyton violaceum. *A*, serpentine appearance of infected hairs present in a follicular crust; × 40. *B*, *C* and *D*, infected hairs, showing involvement of the shaft with large spores arranged in chains. Magnification: *B*, × 180; *C* and *D*, × 355. *E*, typical colony after four weeks. *F*, typical colony showing a corrugated pink sector. *G*, downy surface of a colony growing in the summer. *H*, unusual appearance of spores outside the hair shaft before invasion of the hair; × 170. *I*, culture mount showing simple filaments and no specialized forms.

and usually radial grooves appear near the periphery. In old cultures the color may fade. Pleomorphism is rare.

(e) CULTURE MOUNT.—No free conidia or thyrsi are found. The mycelium is short with numerous septums. Many irregular and bizarre branches are present. In older cultures, chlamydospores are numerous.

(f) FILTERED ULTRAVIOLET RAYS.—An infected hair differs in appearance from a hair infected by one of the Microspora. The dull whitish fluorescence is sometimes difficult to see well because the hairs are embedded in scales. As in most compact growths, the colony is dull but clear. The color is unchanged from that appearing in normal light.

(g) ANIMAL INOCULATION.—Successful transfers of this fungus have been made to many animals, including guinea-pigs, dogs and cats.

(h) DIFFERENTIAL DIAGNOSIS.—On a direct mount of an infected hair, the micro-organism is seen invading the hair shaft. It is to be further differentiated from other endothrices such as A. schoenleini, T. crateriforme and T. sulfureum. Trichophyton violaceum is the most likely endothrix if the infected hair is short and twisted. The differential diagnosis is based on the characteristics of the colony and on the appearance of the culture mount. The favic chandeliers are seen only with A. schoenleini. Both T. crateriforme and T. sulfureum show large numbers of microconidia.

8. TRICHOPHYTON CRATERIFORME

This fungus is found with ringworm of the scalp and with tinea infections of the smooth skin and nails. It is not uncommon in the countries of Western Europe, but it is seldom encountered in this country.

(a) CLINICAL CHARACTERISTICS.—The lesions of the scalp are small and may be few or numerous. These patches show subacute inflammatory changes. On the glabrous skin, crusted, well defined lesions of mildly inflammatory type may develop.

(b) IMMUNOLOGIC REACTIONS.—The intracutaneous test dose of trichophytin usually elicits a vigorous response.

(c) MICROSCOPIC FEATURES.—Large spores in chains are found in the hair shaft. At times the hair appears to be entirely filled with fungous elements.

(d) CULTURAL CHARACTERISTICS.—The colony grows slowly and at prime covers only a portion of an agar slant. The surface of the growth is creamy-white, compact and velvety. The central portion is depressed in an abrupt crateriform manner; this part of the colony is yellowish. Pleomorphism is rare.

(e) CULTURE MOUNT.—Small conidia are noted either on short stocks or

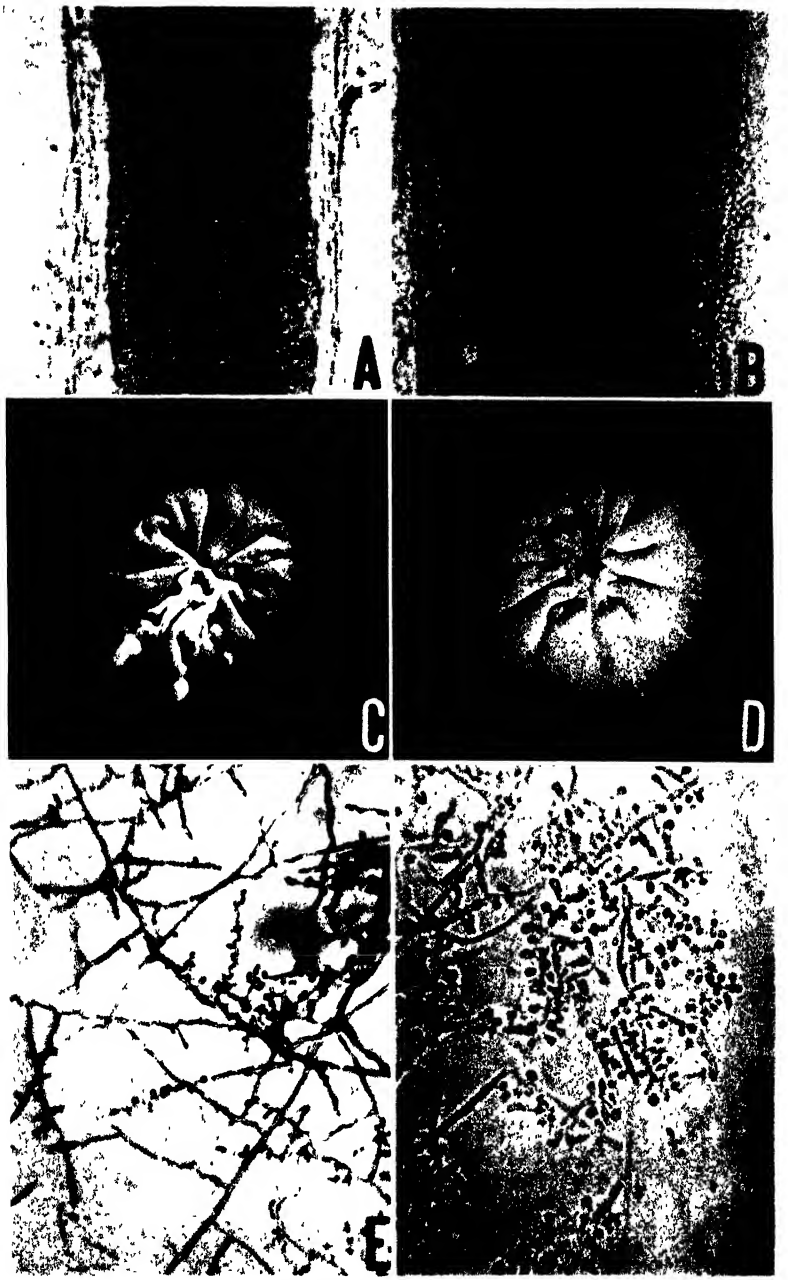

FIG. 82. Trichophyton crateriforme. *A*, infected hair showing spores in the shaft; × 210. *B*, spores closely packed together in the substance of the hair. *C*, colony after one month in the winter. *D*, colony after one month in the summer. (Note the crater and the dense character of the surface growth as compared with the growth in *C*.) *E* and *F*, culture mount showing aleurospores; × 210 and × 410, respectively.

coming directly off hyphae and sometimes in clusters (thyrsi and *grappes*). Chlamydospores are common. Other forms are seldom observed.

(f) FILTERED ULTRAVIOLET RAYS.—Hairs infected with this fungus fluoresce, their appearance being not unlike that of hairs infected with T. violaceum. The cultural growth is clear and bright. The color is dark olive throughout.

(g) ANIMAL INOCULATION.—Guinea-pigs may be inoculated, but the lesions heal spontaneously.

(h) DIFFERENTIAL DIAGNOSIS.—An infected hair reveals an endothrix. The cultural appearance of the endothrices is dissimilar. The culture mounts of T. crateriforme and T. sulfureum show numerous microconidia and are otherwise similar. (See also the preceding section on T. violaceum.)

9. TRICHOPHYTON SULFUREUM

This fungus is infrequently a cause of infections of the scalp or the glabrous skin.

(a) CLINICAL CHARACTERISTICS.—We have observed only two instances of infection with this species. The scalp of a 4 year old girl showed scattered, mildly crusted lesions on the occiput. The lesions were small. The infected hairs were broken off above the surface of the scalp. In the other case, a boy, 9, had a large circinate lesion of the glabrous skin with vesicopustules at the periphery and clearing in the center. An instance of glabrous skin infection with secondary trichophytid was reported by Slaughter and Cawley.

(b) IMMUNOLOGIC REACTIONS.—These are unknown.

(c) MICROSCOPIC FEATURES.—Examination of the hair shows invasion of the shaft, with large spores in linear arrangement. In the circinate lesion, filaments were demonstrated, as in other forms of infection of the glabrous skin.

(d) CULTURAL CHARACTERISTICS.—Growth is moderately fast. The colony is white and fluffy at first, later becoming yellowish gray and more compact. Many radial grooves develop, and central convolutions and wrinkling of the surface are early features. Subcultures may show a colony with less folding, a more fluffy surface and a lighter color, which is almost buff.

(e) CULTURE MOUNT.—Some fuseaux are formed, and quantities of microconidia (thyrsi and *grappes*) will be observed. Chlamydospores are also to be seen.

(f) FILTERED ULTRAVIOLET RAYS.—Pale grayish fluorescence is present when infected hairs are examined. (Compare with Microsporum.)

(g) ANIMAL INOCULATION, and

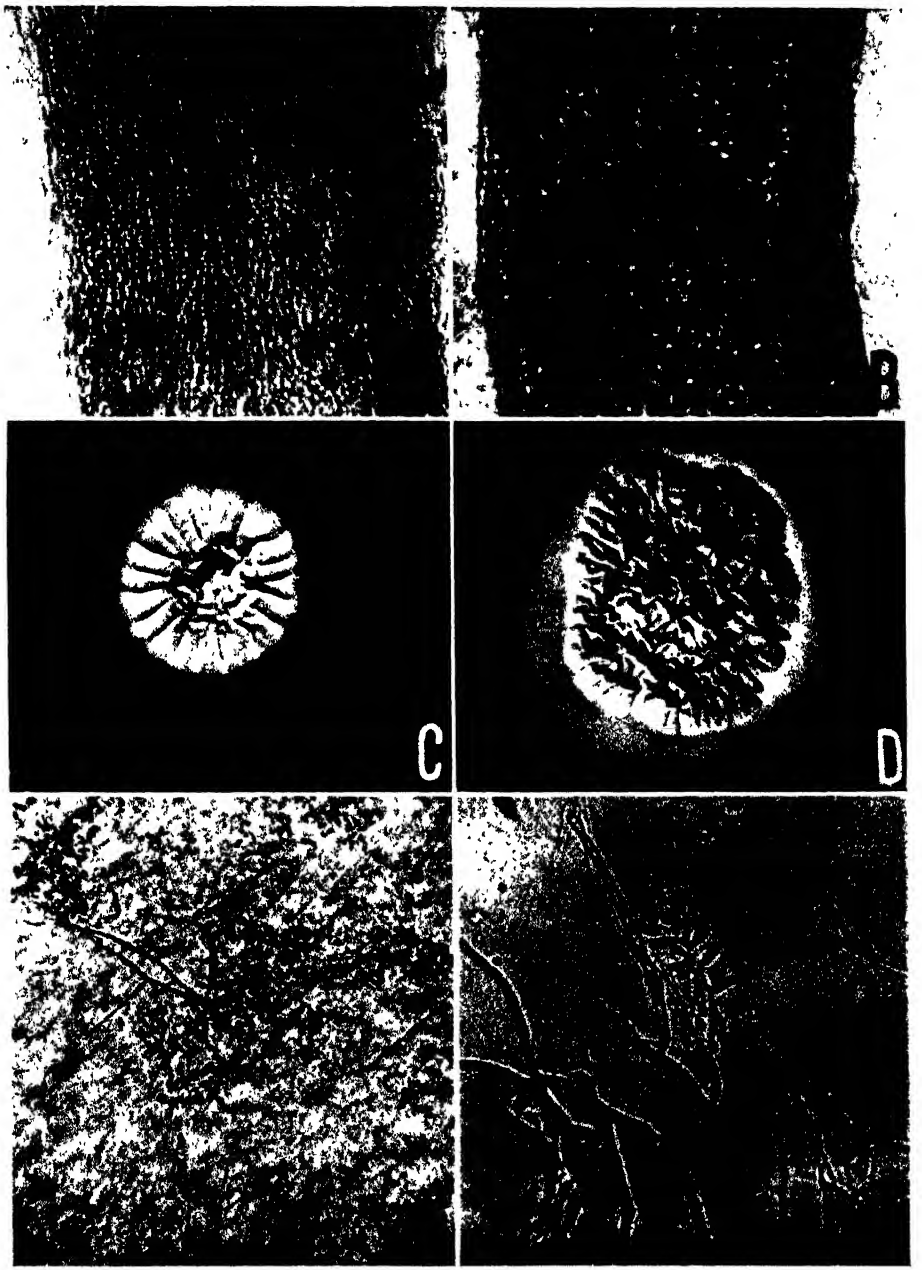

FIG. 83. Trichophyton sulfureum. *A* and *B*, culture mount showing endothrix infection in hairs with a tendency to linear arrangement of the spores; × 225 and × 440, respectively. *C* and *D*, colony after two weeks and six weeks, respectively. *E* and *F*, culture mount from corn meal agar, showing microconidia and fuseaux; × 225 and × 440, respectively.

(h) DIFFERENTIAL DIAGNOSIS.—See the two preceding sections on T. violaceum and T. crateriforme for a discussion of their characteristics.

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10. TRICHOPHYTON GYPSEUM

The chief fungi causing intertriginous infections as well as infections of the nail are T. gypseum and its variants, T. purpureum, and E. inguinale (floccosum). While other species are occasionally isolated from the feet, they are so rare as to be of little practical importance.

At the outset, it should be noted that T. gypseum is unstable and given to the development of variants. It is by no means certain that placing together the various growths in this one species is the final solution. One might consider T. interdigitale (Kaufman-Wolf) to be a pleomorphic form of T. gypseum. Weidman has observed a periodic transition from a fluffy to a powdery and back again to a fluffy condition in a growth isolated from his own toes. Emmons used monospore cultures of M. fulvum from which were produced six types of colonies; these were morphologically different from each other and from the original growth. We have observed that when a granular form of T. gypseum is subcultured it tends to become more fluffy. This change may also be apparent in circumscribed sectors. If material from two sectors is transplanted, the character of each sector is retained. Besides the type usually isolated we recognize three other types which are probably derivatives or at least closely related: (1) a granular type; (2) a white fluffy growth (T. interdigitale), and (3) a white compact growth (T. niveum). Besides the interchanging types of growth (granular or fluffy) which have been noted at different times in cultures of material from the same infection, other evidence has accumulated that the types of T. gypseum mentioned here are closely related. The pigmentation in the subsurface portion of the colony is similar in all types, provided the same batch of dextrose agar is used. This is characteristically a dull rose-tan.

(a) CLINICAL CHARACTERISTICS.—Most of the inflammatory intertriginous and spreading fungous infections of the feet are caused by this species of fungus. The toe nails are also commonly affected, and rarely one or more of the finger nails may be involved. Other intertriginous parts of the body, such as the groin and the axilla, may also become the seat of the disease. Trichophytids produced from intertriginous foci are usually initiated by this species of fungus. The downy types rarely affect hair follicles; the

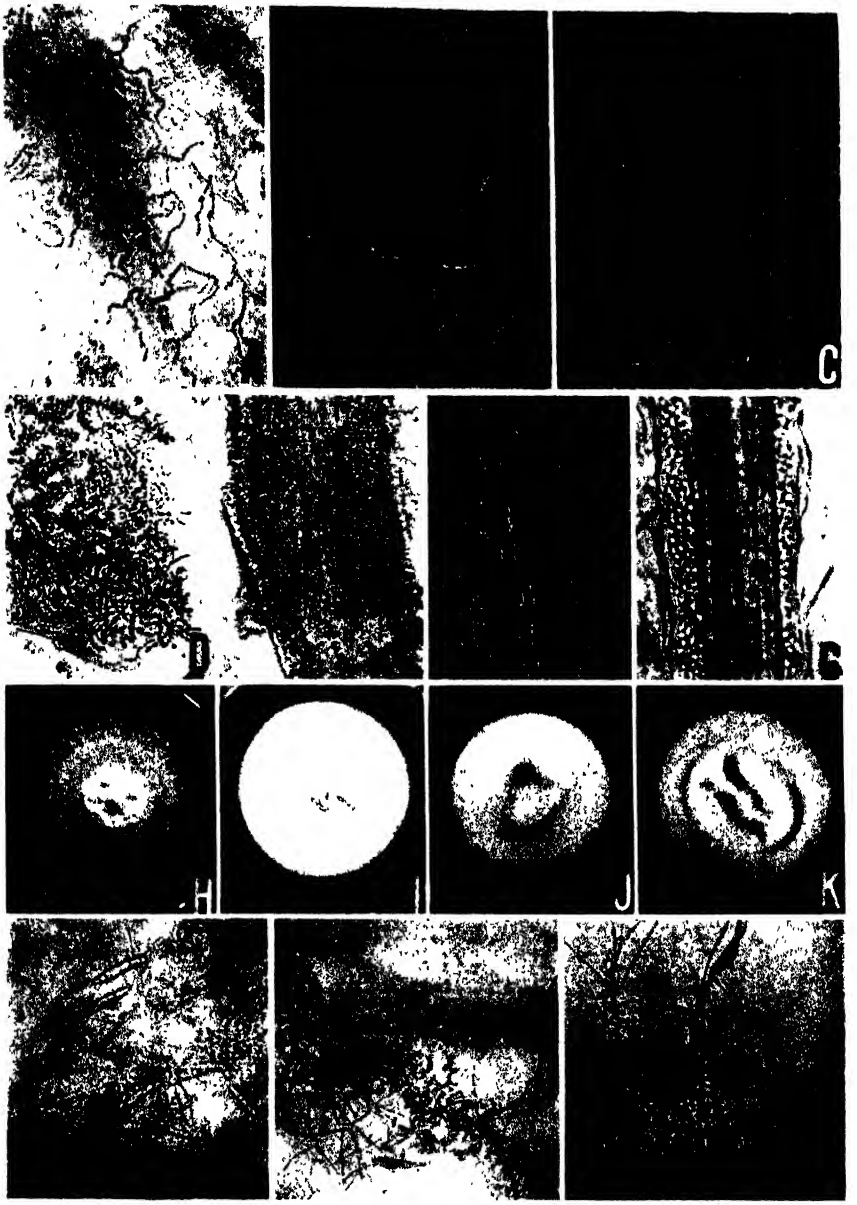

FIG. 84. Trichophyton gypseum. Parts *A* through *G* show the fungus as observed in a direct mount of specimens from *A* and *B*, the skin, × 150 and × 290, respectively; *C* and *D*, nail tissue, × 290 and × 150; *E*, *F* and *G*, infected hairs, with the spores external to the shaft, × 150, × 150 and × 290. The cultural appearance may vary considerably, as shown in *H*, *I*, *J* and *K*. The type of colony seen most frequently is shown in *I*. *L*, a culture mount from a granular colony, such as in *H*, showing microconidia and fuseaux in abundance; × 150. *M* and *N*, culture mount from a colony of the variety usually isolated (*I*), showing spores of the same type but in smaller numbers; spirals may also be seen; × 150 and × 290.

granular or powdery varieties may produce follicular infections of the scalp and other parts of the body of acutely inflammatory nature. T. gypseum is one of the causes of kerion.

(b) IMMUNOLOGIC REACTIONS.—Patients who show a primary inflammatory reaction to this fungus also react to trichophytin. It is our impression (our experience is yet too limited to be certain) that the powdery type sensitizes the skin to a greater degree than the fluffy type and that allergic reactions (ids) are more common with the powdery type.

(c) MICROSCOPIC FEATURES.—Trichophyton gypseum is an ectothrix Trichophyton; the fungus is external to the hair, and the spores tend to form chains. The spores are similar in size to those of the Microspora. In scales, macerated skin and nail tissue the organisms appear as chains of spores or as segmented mycelium with little branching.

(d) CULTURAL CHARACTERISTICS.—(1) The type usually isolated appears first as a white and fluffy growth. After 10 days to two weeks the surface becomes velvety, flat and light buff or buff-yellow. There is usually a boss at the center, and occasionally there are a few irregular folds. (2) The granular or powdery type of growth is characterized by its powdery or velvety surface, with fluffy changes developing as it ages. The color is light buff or maize-yellow. The rate of growth is moderately fast. (3) The white fluffy type of culture (T. interdigitale) begins as a downy feather-like projection; the growth rapidly develops and within two weeks almost covers an agar slant. It is almost pure white. The growth shows many aerial hyphae. (4) The white compact type (T. niveum) at first grows out white and fluffy. The surface then becomes compact, and irregular elevations and depressions make their appearance. The snow-white color is retained.

(e) CULTURE MOUNT.—(1) The ordinary type is characterized by spirals. Fuseaux with blunt ends are present in small numbers. Nodular organs, pectinate bodies, racquet mycelium and chlamydospores are also to be noted. The mycelium is septate and usually branched. Microconidia are also to be seen as thyrsi and as *grappes*. (2) The granular type shows few spirals. There are numerous blunt-end fuseaux with dense masses of microconidia produced in *grappes* and thyrsi. Chlamydospores and racquet mycelium are also present in the subsurface growth. (3) In the fluffy type (T. interdigitale) the aerial growth consists of a large percentage of vegetative filaments. There are limited numbers of microconidia in small clusters. Nodular organs and racquet mycelium may be found. Spirals and fuseaux are usually absent. (4) In the white compact type (T. niveum) the findings are essentially the same as in the fluffy type.

(f) FILTERED ULTRAVIOLET RAYS.—There is no fluorescence to be detected when follicular infections caused by ectothrix Trichophyta are examined

under filtered ultraviolet rays. Fungi in nails, scales or macerated tissue do not show any fluorescence. In culture, the granular type is typically bright and clear and shows concentric bands of color, beginning with a light soft blue-violet in the center. The edge is fawn-colored. With the compact and fluffy types the color of the entire colony is bright indistinct mauve. The T. niveum type has a yellow tone throughout.

(g) ANIMAL INOCULATION.—The granular type of organism is inoculable into guinea-pigs, dogs, cats and rabbits. The fluffy types have probably lost their pathogenicity for these animals.

(h) DIFFERENTIAL DIAGNOSIS.—When T. gypseum invades a hair follicle, it produces considerable inflammation. The hairs are not broken, but they may lack color. The fungi are not found in the shaft. The spores are in linear formation and sparse, in contrast to those of species of Microsporum. In examination of scales and macerated tissue it is difficult and at times impossible to determine species. On culture, T. purpureum must be differentiated. The initiation of growth is faster in all types of T. gypseum. In the ordinary type of T. gypseum the central fluffy portion is smaller than in T. purpureum. In the fluffy type of T. gypseum the aerial hyphae are most luxuriant, often being present on the sides of the tube. The fluffy form of T. purpureum grows up in a hemispheric mass but is never seen along the test tube. The color of the pigment is different in T. purpureum and in T. gypseum. In the former it appears earlier and is deep rose-purple. In the latter, the color is seen in older colonies and is dull rose-tan. The difference between culture mounts of these two species is frequently difficult to determine. In T. purpureum we have never seen spirals and have noted few fuseaux.

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11. TRICHOPHYTON PURPUREUM (BANG)

Trichophyton purpureum (Epidermophyton rubrum [Castellani], Trichophyton rubidum [Priestly], etc.) is frequently found in the tropics and is also found in China and Japan; it is common in the southern part of the United States. It often causes superficial fungous infections in New York.

(a) CLINICAL CHARACTERISTICS.—Few fungi are responsible for a more typical clinical picture. The eruption may be localized or extensive. In

either case, the manifestation is usually mildly inflammatory, the affected skin being dull red, scaly and thickened. The interdigital webs, the sides of the feet, the inner surfaces of the thighs, the hands and the nails of either the hands or the feet or both are the usual sites. Many patients complain of severe itching not confined to the areas of the eruption. Uncommonly, the smooth skin shows erythematous plaques or widespread gyrate lesions.

(b) IMMUNOLOGIC REACTIONS.—The usual delayed reaction to trichophytin is slight or absent in patients with an infection due to T. purpureum. There is sometimes an immediate wheal response (see Chapter XXX, "The Trichophytin Test").

(c) MICROSCOPIC FEATURES.—Relatively few fungous filaments are noted. Repeated tests may be needed to demonstrate presence of fungus. When the hair follicle is invaded the fungus is seen to be an ectothrix Trichophyton.

(d) CULTURAL CHARACTERISTICS.—In the primary growth, the culture at first is fluffy, pure white and hemispheric. Later the edge of the colony is less fluffy, becoming almost velvety. Sometimes the central umbo is lacking. Radial grooves may appear. The back of the colony soon develops a typical rose-purple color. This color gradually spreads to the edge of the older colony and may later be noted in varying degree throughout the colony.

If the aerial growth is abundant, the colony appears white and fluffy and the rose-purple color can only be seen from the back. When the growth is more sparse the color may be seen from the top. This accounts for many of the variations in the color of the colony. The appearance of the colonies with a minimal aerial growth varies from powdery to granular.

(e) CULTURE MOUNT.—Vegetative filaments are simple and show little variation. The microconidia are produced in *grappes* or along the mycelium as hyphae sporiforae. In fluffy colonies microconidia predominate. There is little evidence of fuseaux (except when they are searched for). In granular colonies abundant fuseaux may be seen, and microconidia are scant. Racquet mycelium and chlamydospores will be observed if the nutrition of the medium is reduced.

(f) FILTERED ULTRAVIOLET RAYS.—Without experience one has difficulty in distinguishing between T. gypseum and T. purpureum. In an early colony of T. purpureum the color is a bright, light blue, which is present throughout the colony or, if the colony is very fluffy, at the periphery alone. In older colonies the light blue border is characteristic.

(g) ANIMAL INOCULATION.—This is occasionally successful. Reiss, working in our laboratory, found that rabbits which had been castrated or had received x-ray exposures to the abdomen could be infected at will.

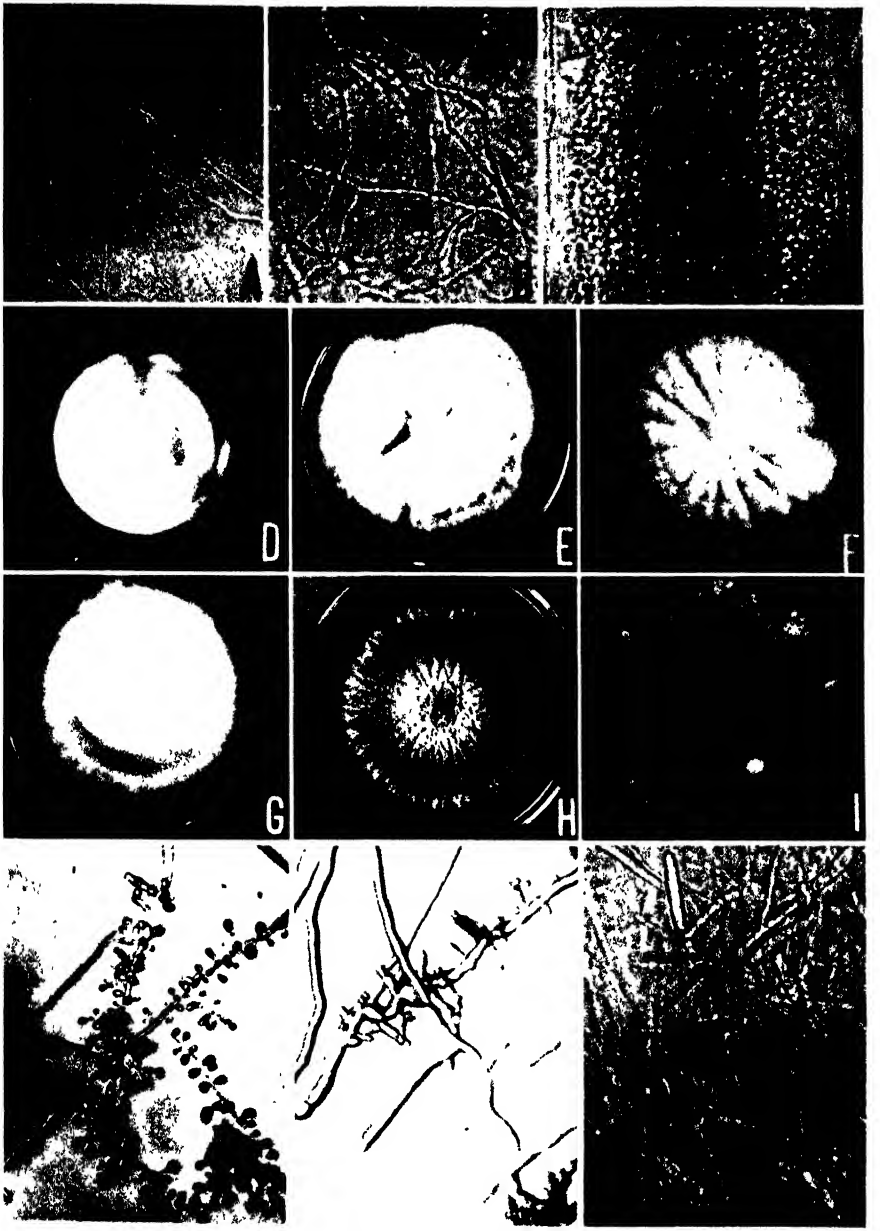

FIG. 85. Trichophyton purpureum. Appearance of the fungus in a direct preparation from *A*, skin; *B*, fingernail, and *C*, hair from a follicular lesion on the leg. The cultural growths in *D*, *E*, *F*, *G*, *H* and *I* show wide variations from thick fluffy growths to thin granular colonies. The clinical involvement was of the same character despite the differences in the appearance of the growth on culture. The culture mount shows microconidia and fuseaux, as noted in *J* and *K*. In *L* the mount from a granular colony (*H*) shows numerous fuseaux. Microconidia were also present. (Magnification of all photomicrographs, × 305.)

(h) DIFFERENTIAL DIAGNOSIS.—The main species of fungus to be differentiated is T. gypseum. The cultural growth of T. purpureum is typical when starting and developing, and the tinctorial changes are characteristic. (See also the preceding section on T. gypseum.)

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12. EPIDERMOPHYTON INGUINALE (EPIDERMOPHYTON CRURIS; EPIDERMOPHYTON FLOCCOSUM)

This organism is found sporadically in various parts of the world. It is capable of producing epidemics in institutions, in camps, on ships and elsewhere. It is said to be more common in the tropics and is known in India as the organism which causes dhobie itch.

(a) CLINICAL CHARACTERISTICS.—This species of fungus has never been found as a follicular invader. The classic location for the eruption is the upper inner surfaces of the thighs, but the axillae, the interdigital webs and other parts of the feet and other areas of the smooth skin may be affected. In two instances we have isolated this fungus from scaly lesions on the hands. Usually the affected skin is not primarily severely inflamed, and macroscopic vesiculation is rarely noted. The affected skin is sharply marginated and red, with little tendency to central clearing. The surface is scaly, and sometimes the scaling is so abundant that only slight erythema is observed. Small satellite lesions are characteristic. There may be maceration on the webs of the toes; less frequently, vesicopustules may be found on the soles. Tinea unguium is rarely if ever caused by this organism.

(b) IMMUNOLOGIC REACTIONS.—There are seldom strong reactions to trichophytin. Reactions are moderate or, more commonly, mild or even negative.

(c) MICROSCOPIC FEATURES.—Chains of spores in which the elements tend to be flattened are frequently noted in fairly large numbers. When the scaling is profuse, large amounts of fungous material will be observed.

(d) CULTURAL CHARACTERISTICS.—Growth begins slowly and may not be apparent for two or three weeks. It then continues at a moderate rate. The colony has a velvety or felted surface with irregular folds and grooves; at times the surface may be smooth. The aerial hyphae are few. The color is characteristically grayish olive-drab but sometimes is greenish drab. Pleomorphic growth, as evidenced by whitish tufts, is common, appears early and may eventually cover the entire agar slant.

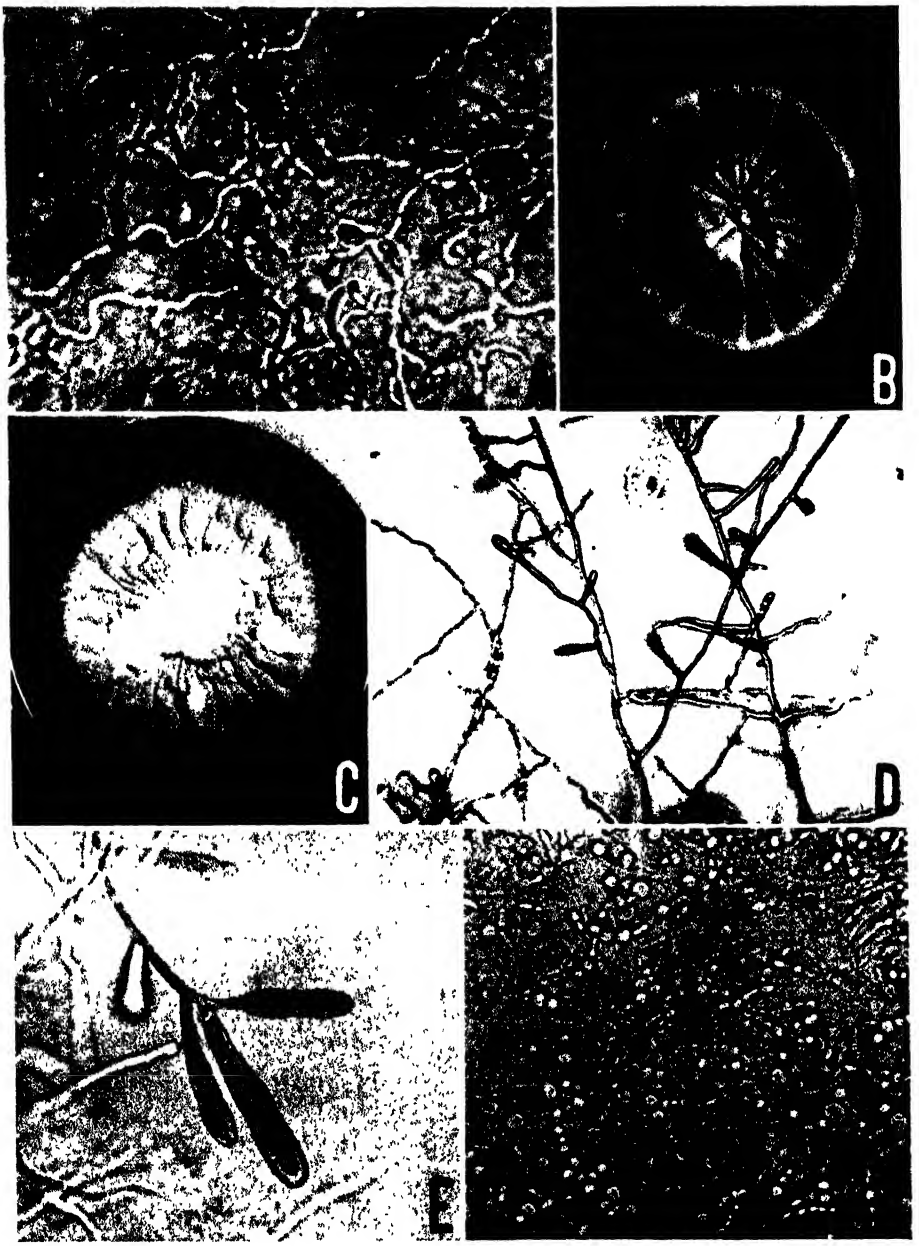

FIG. 86. Epidermophyton inguinale. *A*, numerous wavy filaments present in a direct mount from the scales. *B*, colony after two weeks. *C*, colony after six weeks, showing pleomorphic tufts and fringe. *D*, culture mount, × 200. *E*, culture mount showing blunt-end fuseaux; × 400. *F*, chlamydospores, present in abundance in the vegetative portion of the colony; × 200.

(e) CULTURE MOUNT.—Club-shaped fuseaux with blunt ends in groups resembling bunches of bananas are frequently found in specimens from the growth with a fluffy surface. Chlamydospores are abundant in the subsurface part of the colony. Racquet mycelium is often seen, but other vegetative and reproductive forms are infrequent.

(f) FILTERED ULTRAVIOLET RAYS.—In about two weeks the colony is clear, dull and dark olive.

(g) ANIMAL INOCULATION.—Animal inoculation is not successful.

(h) DIFFERENTIAL DIAGNOSIS.—In a direct mount, if the filaments are numerous, infection with E. inguinale may be surmised. The cultural growth can hardly be confused. The finding of clusters of fuseaux with blunt ends in a culture mount is characteristic.

13. MONILIA (CANDIDA) ALBICANS

This is a pathogenic yeastlike micro-organism of considerable importance.

(a) CLINICAL CHARACTERISTICS.—The manifestations of this organism may be cutaneous (localized, generalized) or systemic. The localized eruptions include perlèche, erosio interdigitalis blastomycetica, paronychia and onychia and intertrigo of the toes and of the inframammary, axillary, inguinal, intergluteal, anal and umbilical regions, as well as eczematous patches on the smooth skin. The generalized types include any or all of the manifestations just mentioned, with additional involvement of the scalp, eyelids or other areas of skin. The intestinal tract of a patient with cutaneous moniliasis, as well as that of a patient with no cutaneous manifestations, frequently harbors the organism. The percentage of patients with stool cultures yielding M. albicans increases with the age of the patients. Thrush, smooth tongue and other intraoral conditions are caused by this yeast. Monilia albicans probably causes fermentation in the intestinal tract with production of gas in many otherwise normal persons. This organism has also been considered capable of causing a vaginal discharge, and very occasionally an infection of the lungs and bronchi simulating atypical tuberculosis.

(b) IMMUNOLOGIC REACTION.—In only 57 per cent of patients with the localized form of cutaneous moniliasis and in only 52 per cent of patients harboring the organism in a lesion of the skin or of the gastrointestinal tract is there a positive response to the intracutaneous test with a commercial extract of M. albicans. Of patients without any obvious infection, from 46 to 54 per cent have a similar positive reaction. For this reason the test appears to be of limited diagnostic value. With increasing age, the percentage of reactions to the test increases: thus in the decade between

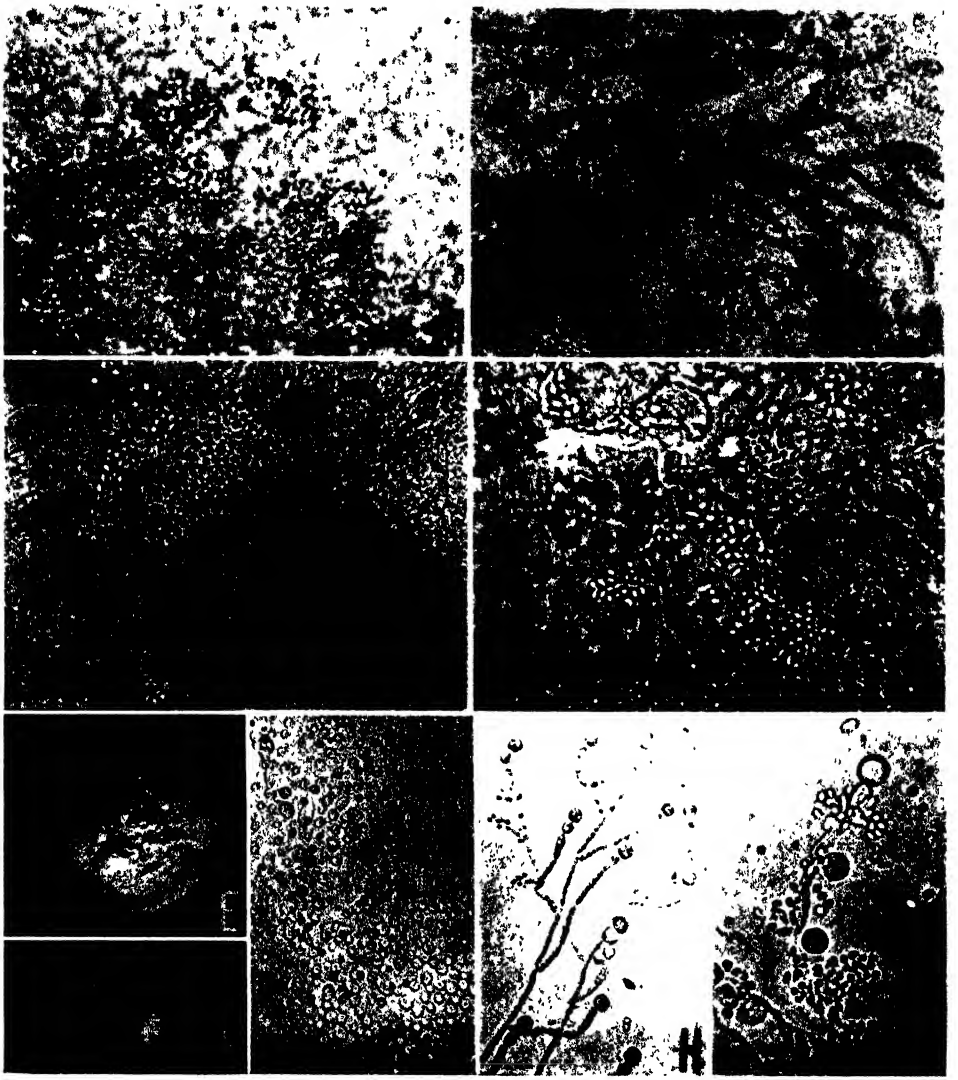

FIG. 87. Monilia albicans. Appearance of the fungus on direct examination. The organism was isolated from lesions of *A*, erosio interdigitalis blastomycetica; *B*, oral thrush; *C*, paronychia, and *D*, intertrigo in the inguinal region. *E*, giant colony, showing pasty growth and multiple craters in the center. *F*, young primary culture. *G*, direct mount from culture, showing variations in the size of cells; × 335. *H*, development of chlamydospores and filaments on corn meal agar; × 245. *I*, mount from an older colony, showing clusters of budding cells and chlamydospores; × 445.

51 and 60 years inclusive, 75 per cent of apparently normal persons show a cutaneous reaction to the injection of an extract of M. albicans.

(c) MICROSCOPIC FEATURES.—In material from some untreated lesions, such as those of thrush or erosio interdigitalis blastomycetica, a tangled network of fine mycelium with clusters of spores may be noted. In scrapings from nails and many other locations, only a few hyphae or budding cells may be observed, and frequently the results from the potash preparation are uncertain.

(d) CULTURAL CHARACTERISTICS.—The growth on dextrose agar is moderately fast and is first noted after two or three days. It is wet, pasty and cream-colored. The surface is usually smooth except near the center of the colony, where it has a honeycombed appearance due to ruptured air bubbles. On corn meal agar, a deep stab with a needle containing the cultural growth results in the characteristic picture of an inverted pine tree. It is notable that pure cultures are the rule. It seems that there is marked inhibition of other micro-organisms in the presence of M. albicans.

(e) CULTURE MOUNT.—Mycelial development is best seen in material from colonies grown on corn meal agar. Clusters of spores in rounded masses are to be observed along the hyphae, and chlamydospores also develop. No ascospores are present.

(f) FILTERED ULTRAVIOLET RAYS.—The appearance of colonies changes little from their appearance in normal light; the color is clear, dull and yellowish brown.

(g) ANIMAL INOCULATION.—Intracutaneous inoculation in guinea-pigs causes a mild inflammatory reaction. Rabbits are killed by the intravenous injection of 1 cc. of the 1:1,000 suspension, miliary abscesses being produced in all parts of the animal (Benham).

(h) FERMENTATION REACTIONS.—Acid and gas are produced with dextrose, levulose and maltose but not with saccharose (Benham).

(i) AGGLUTINATION REACTIONS.—Agglutination is seen when a serum is prepared against a known strain of the yeast (Benham).

(j) DIFFERENTIAL DIAGNOSIS.—Cryptococci do not develop mycelium, and other fungi in the monilia group may be distinguished from M. albicans by the absence of chlamydospores when they are grown on corn meal agar. Mycoderma may usually be recognized by its gross appearance in culture; a culture mount reveals arthrospores. Endomyces and Saccharomyces form ascospores; the former also develops mycelium.

14. MALASSEZIA FURFUR (MICROSPORUM FURFUR)

This is the cause of tinea versicolor, and either this fungus or one closely related is the source of some cases of tinea flava and achromia parasitaria.

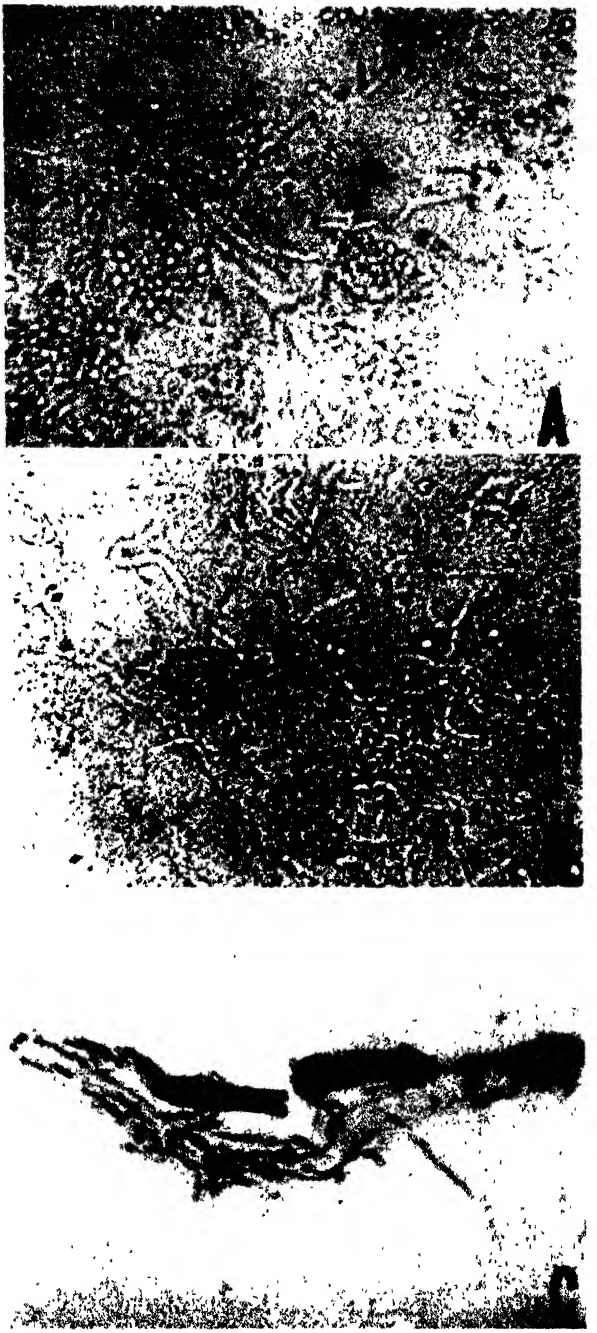

FIG. 88. Malassezia (Microsporum) furfur. *A* and *B*, appearance on direct examination of scales, showing short filaments and groups of spores with double-contoured walls; × 415. *C*, histologic section showing the fungous elements in the stratum corneum.

(a) CLINICAL CHARACTERISTICS.—Tinea versicolor is a superficial scaly eruption with yellowish to brown color, favoring the trunk and usually seen in young adults. Fluorescence may be noted when the rash is examined under filtered ultraviolet radiation. An interesting feature is the frequent appearance of pseudo-achromia at the site of the eruption after injudicious exposure to solar radiation.

(b) IMMUNOLOGIC REACTIONS.—No sensitization of the skin has been demonstrated.

(c) MICROSCOPIC FEATURES.—The facility of diagnosis is rarely approached even occasionally with specimens from any other mycosis. The scales may be examined as soon as the potash preparation is made. There is usually an abundance of material consisting of spherical or ovoid refractile spores in groups or clusters. Mycelium is seen in considerable numbers as wavy threads of moderate length. Branching may be noted. The filaments are readily broken up when one is making the mount. When scales are removed from the surface of patches of pseudo-achromia, only a few spores, without appreciable grouping, may be noted. Filaments are usually few; they consist of short rods.

(d) CULTURAL CHARACTERISTICS.—A number of investigators have reported success in culturing the organism, but so far there is no general agreement. Moore described experiments in which he obtained cultural growths on many different mediums after the initial isolation on maltose broth. He was able to inoculate three of eight human volunteers when no laboratory animal was susceptible. In addition to proving with the usual evidence that a given culture is pathogenic for animals or for human volunteers, it appears essential to note fluorescence under filtered ultraviolet rays, of the cultural growth and of the lesion experimentally produced, since fluorescence is characteristic of M. furfur. This observation has not yet been reported.

(e) FILTERED ULTRAVIOLET RAYS.—The rash caused by M. furfur fluoresces either a light or a dark brown according to the degree of pigmentation present. The usual color is golden yellow. The appearance of the cultural growth is unknown.

(f) ANIMAL INOCULATION.—Ordinary laboratory animals appear immune to the fungus applied in scales. Cultural growths would be essential to a definite decision of this point.

(g) DIFFERENTIAL DIAGNOSIS.—The presence of clusters of spores (apparently with double-contoured walls) and of fragmented mycelium (usually abundant) provides a characteristic picture. In M. albicans the filaments are more slender and dense masses of spores (sometimes budding) are a distinguishing feature.

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15. ACTINOMYCES MINUTISSIMUS (MICROSPORUM MINUTISSIMUM)

This is the micro-organism causing erythrasma.

(a) CLINICAL CHARACTERISTICS.—Erythrasma is characterized by superficial scaly plaques, well demarcated from normal skin by a reddish border. The lesions are yellowish to brown. The disease is usually localized to one or both of the axillae or the groins or to other intertriginous parts.

(b) IMMUNOLOGIC REACTIONS.—There is no sensitization to trichophytin. Sensitization to the cultural organism has been reported, but this is questionable.

(c) MICROSCOPIC FEATURES.—The scales may be examined after the slide is stained (see p. 236). The fungous elements are too small to be seen under the usual low power magnification. Under high power magnification one may make out fine threads. On examination with the oil immersion lens, the threads appear long, tortuous and interlacing; segmentation may be noted. A few round spores may be seen. Granules are occasionally visible.

(d) CULTURAL CHARACTERISTICS.—We have not been able to grow the organism on artificial mediums. According to Poehlmann, however, several investigators have been able to do this.

(e) FILTERED ULTRAVIOLET RAYS.—The rash caused by this micro-organism does not fluoresce, its appearance being similar to that observed in ordinary light. The appearance of the cultural growth is unknown.

(f) ANIMAL INOCULATION.—We have not had any personal experience.

(g) DIFFERENTIAL DIAGNOSIS.—The micro-organism is so small that it may be mistaken for an incidental bacterial contaminant. No other species of fungus can be confused with it.

16. ENDODERMOPHYTON TROPICALE

This is the chief cause of tinea imbricata. Other fungi also reported to be pathogens (E. indicum and E. concentricum) are probably variants.

(a) CLINICAL CHARACTERISTICS.—Tinea imbricata is a superficial mycosis seen commonly in the tropics and in some temperate zones such as North China (F. Reiss). It is characterized by pruritic ringed lesions and profuse scaling. The nails may be involved. The hair follicles are never invaded, and suppuration is unknown.

FIG. 89. Actinomyces minutissimus. Stained slide showing interlacing filaments. Photographed through oil immersion objective; × 1000.

(b) MICROSCOPIC FEATURES.—Numerous interlacing segmented hyphae are present in scales.

(c) CULTURAL GROWTH.—Scales should first be soaked in alcohol for five to 10 minutes and then placed in dextrose broth. Many tubes become contaminated with bacteria. In tubes free from contamination, a few mycelial filaments appear. After several weeks the fluffy mass may be transferred to a solid medium. There is some resemblance to A. schoenleini. The growth is compact and gray to brown, with an uneven surface.

(d) CULTURE MOUNT.—Vegetative forms are numerous. Arthrospores but no microconidia are present.

(e) ANIMAL INOCULATION.—Reiss and Tshu were unable to inoculate rats, guinea-pigs and rabbits.

(f) FILTERED ULTRAVIOLET RADIATION.—The appearance is unknown; we have had no experience.

(g) DIFFERENTIAL DIAGNOSIS.—The filaments are reputedly more numerous and are located deeper in the epidermis than with Trichophyton. The cultural growth is glabrous, and this together with the tinctorial changes will serve to rule out other fungi.

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17. HORMODENDRUM PEDROSOI

Many species of Hormodendrum are found as common saprophytes. This micro-organism is one of the three fungi established as causes of chromoblastomycosis and is that most frequently isolated. The fungus was isolated by Pedroso in Brazil; he delayed the report until 1920. It was first thoroughly described by Brumpt in 1922 and later by others.

(a) CLINICAL CHARACTERISTICS.—The lesions of chromoblastomycosis are usually found on the lower extremities. The disease may begin as a nodule; the process slowly extends to adjacent skin, and when it is well developed, nodules, ulcers and verrucous elevations are to be found. The nodules may be violaceous; a brownish color is characteristic. The disease may slowly progress over many years, when large, elevated cauliflower-like tumors may develop. There is no apparent tendency to systemic involvement.

(b) IMMUNOLOGIC REACTIONS.—Conant and Martin found complement-fixing antibodies in the serums of immunized rabbits. There was also a high titer for another species of Hormodendrum, H. compactum.

(c) MICROSCOPIC FEATURES.—Pus removed from fresh lesions may be examined. So-called sclerotic cells (Medlar), which may be septate and

usually occur in groups, are typical. Small septate filaments may also be noted. Budding is never seen as reproduction takes place by division.

(d) CULTURAL CHARACTERISTICS.—After four weeks the colony on dextrose agar has the shape of a low cone and a diameter of about 45 mm. The margin is even. The surface is covered with a grayish nap. Zonation may appear. Thus, successively from the center to the periphery, a typical colony presents concentric zones of olive-black, brownish olive, olive-black, brownish olive, olive-black, olive-gray and gray. The colors vary somewhat according to the underlying mycelium and the degree of sporulation. After two or three months the colonies are brown.

(e) CULTURE MOUNT.—A branched or unbranched conidiophore bears brownish-olive spores at the tip and, in later cultures, on the sides as well. A secondary and occasionally a tertiary spore may form from the first spore. Spores sometimes appear in branching conidial chains. The spores may vary considerably in size and shape. Disjunctors, defined by Emmons and Carrión as "the narrowed end of the spore and the thickened wall which surrounds and terminates it," are usually to be found. In a specimen from old cultures or in one grown on corn meal agar, the phialophora type of conidiophore may appear. It is bottle-shaped, being restricted where the spore is formed. Above this the wall flares, forming a cup from which conidia are extruded.

(f) FILTERED ULTRAVIOLET RADIATION.—There is no change in color, the black being more intense. No fluorescence is to be noted.

(g) ANIMAL INOCULATION.—Characteristic lesions are produced in rats. Emmons and Carrión found that several saprophytic species of Hormodendrum were also pathogenic for rats, with only mild lesions. Azulay could inoculate his strain into the testes of guinea-pigs and white rats.

(h) DIFFERENTIAL DIAGNOSIS.—Acrotheca and Trichosporum may be readily excluded by the observation of branching chains of spores.

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18. HORMODENDRUM COMPACTUM

Carrión isolated this micro-organism in 1936 from lesions suggesting psoriasis and lupus erythematosus which were limited to an arm. In places

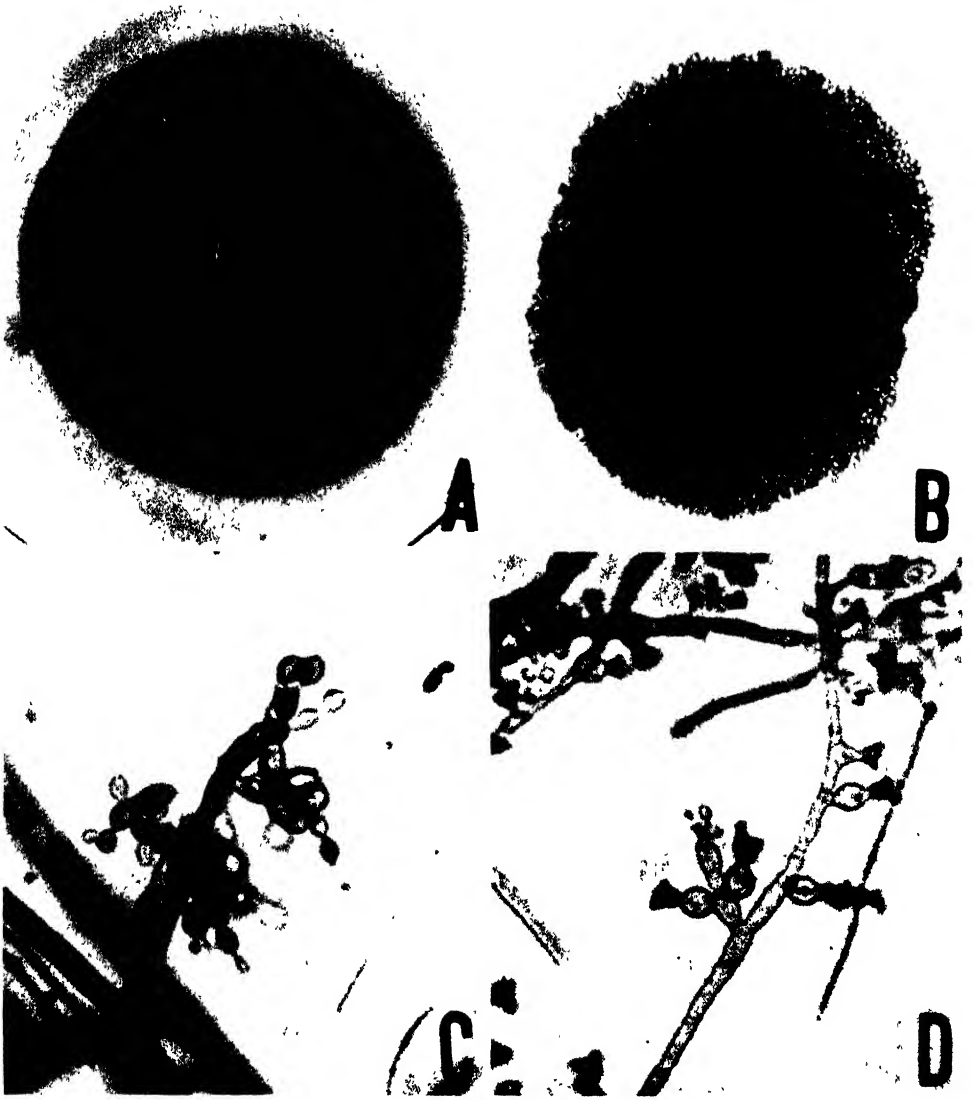

FIG. 90. Hormodendrum pedrosoi. *A*, colony after two months. *B*, mount from a young colony, showing simple yeastlike cells; × 130. *C*, culture mount showing the youngest spore at the tip of the chain of spores; × 1000. *D*, culture mount from an older colony, showing cup-like conidiophores of the Phialophora type; × 1000.

the rash appeared hypertrophic, and considerable scarring was present. The organism was demonstrated in scales removed for examination. This fungus grossly resembles H. pedrosoi on artificial mediums, but it grows more slowly, the surface is irregular and uneven, and the border is indented. The culture mount shows H. compactum (still in comparison with H. pedrosoi) to have coarser mycelium, thicker cell walls and more pigment. Branching occurs at sharper angles, and there are several other points of differentiation. The appearance under filtered ultraviolet rays is similar to that noted for H. pedrosoi.

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19. PHIALOPHORA VERRUCOSA

This micro-organism is an infrequent cause of chromoblastomycosis. In the United States it was first isolated from a patient in Boston in 1915, and the only other cultivation was obtained from a patient in Texas. The fungus has also been found in South America.

(a) CLINICAL CHARACTERISTICS.—The lesions produced by this fungus may be similar to those caused by H. pedrosoi. In Lane's case (Boston) the lesions consisted of an ulcer and a nodule localized to a buttock. The patient in Texas, however, exhibited an eruption similar to that usually observed in South America.

(b) CULTURAL CHARACTERISTICS.—The growth is greenish brown; it is covered with a short nap and has a grayish border.

(c) CULTURE MOUNT.—This reveals typical flask-shaped conidiophores.

(d) FILTERED ULTRAVIOLET RAYS.—The appearance is similar to that noted for H. pedrosoi.

(e) IMMUNE REACTIONS.—Conant and Martin found complement-fixing antibodies in the serums of rabbits immunized with a strain of P. verrucosa.

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20. ACTINOMYCES BOVIS (HARTZ; WOLFF AND ISRAEL)

The Actinomycetes at times resemble bacteria and at other times, molds, and have been considered by some to be parent forms from which both branches evolve. Their exact classification is still unsettled.

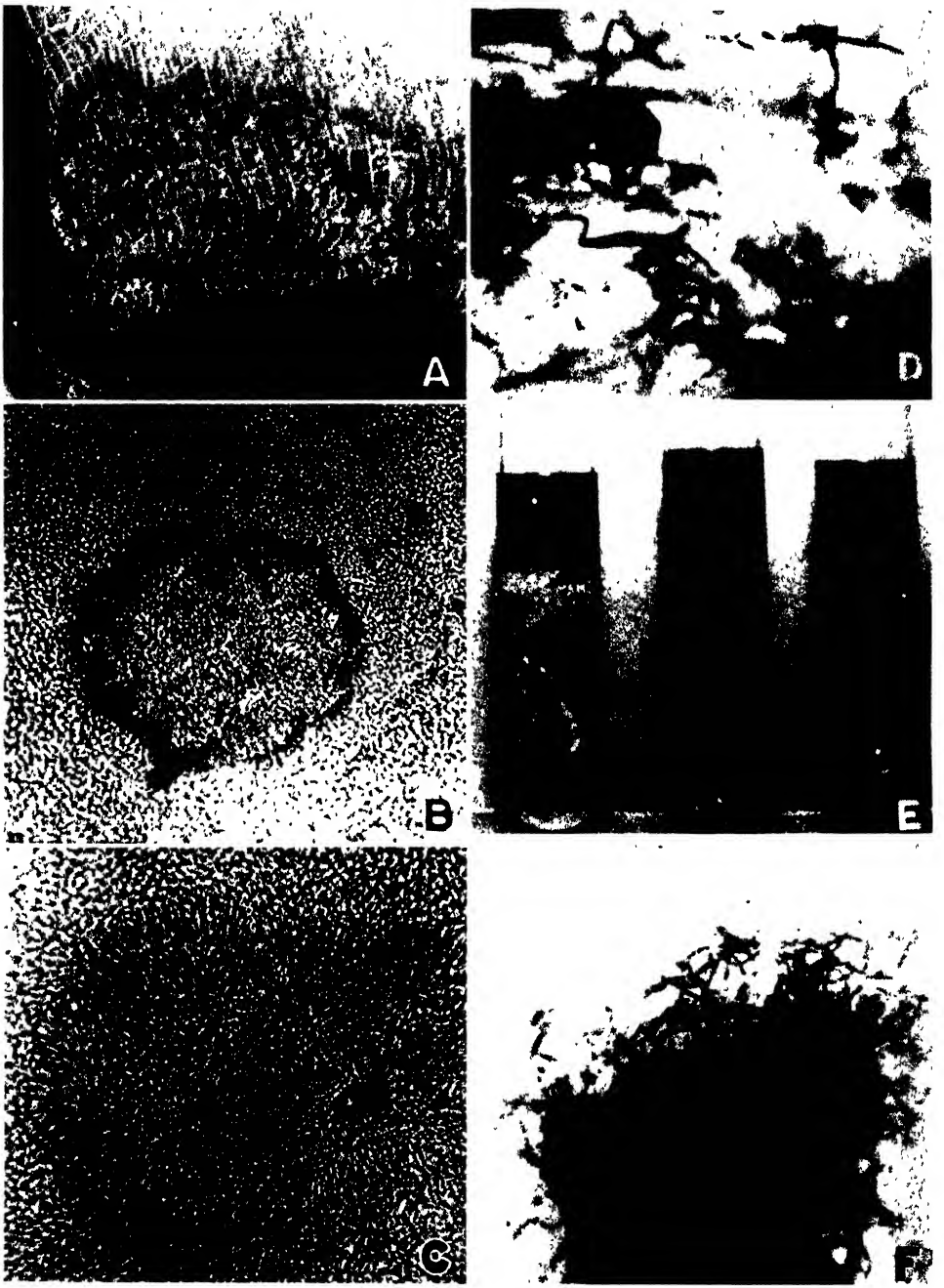

FIG. 91. Actinomyces bovis. *A*, granules caught in gauze dressing from draining sinus; × 2. *B* and *C*, granules of A. bovis; × 200 and × 400. *D*, crushed granule, which is gram-positive; × 1500. *E*, five day cultures in anaerobic medium using sodium thioglycollate. *F*, culture mount, showing acid-fast matted rods; × 1500.

Other Actinomycetes are said to cause actinomycosis in some cases, but A. bovis is probably the chief offender. The clinical characteristics, the etiology and other features of actinomycosis have been described in Chapter X, pp. 177 ff.

(a) IMMUNE REACTIONS.—Agglutination reactions are usually positive. There is a cutaneous hypersensitivity to vaccine in patients with the infection.

(b) MICROSCOPIC FEATURES.—In making a diagnosis of actinomycosis, one relies chiefly on the search for the ray fungus in pus from a suspected lesion. If pus is not exuding freely from a sinus tract, gentle pressure usually causes some to appear. Occasionally it is necessary to wait for a day or two for pus to form, and this is usually preferable to irrigating a sinus tract. If pus is scanty, gauze drains may be inserted in the sinus tract or a gauze pack applied to the site. After 24 hours granules will probably be found enmeshed in the material. In the diagnosis of actinomycosis of the lung, the presence of granules in a direct smear of sputum indicates an active infection. The observation of Actinomyces on culture may be misleading, as it is frequently present in the buccal cavity as a saprophyte.

The specimen of pus is placed on a slide, and over this a cover slip is dropped. If a granule is present, it may be detected under the low power of the microscope. For details of structure, higher magnification is necessary. For a permanent mount a drop of pus containing a granule is placed on a large cover slip and covered with a smaller cover slip. Glycerin may be run under the smaller cover slip to replace pus and air. When the glycerin has had time to permeate the preparation and the cover slips have flattened as much as they will (several days), the cover slip preparation may be attached to a glass slide by means of balsam inverted so that the smaller cover slip is nearest the slide. If one wishes to bring out minute details, the granule may be stained with Gram's stain or with carbolfuchsin before the addition of glycerin.

The granule consists of one or more colonies, each of which contains twisted mycelium with pigment granules in the central zone and a palisaded arrangement of organisms forming a fringe at the periphery. These latter organisms are noted for an enlargement at one end (the so-called club form), and they are also striated. There are no spores. The ray fungus is gram-positive. The central mycelium takes the basic dye, and the peripheral zone takes the acid dye.

(c) CULTURAL CHARACTERISTICS.—It is usually necessary to begin growth on an anaerobic medium, preferably one containing blood or meat. Emmons recommended dextrose-veal infusion agar. We have found the anaerobic medium recommended by Brewer to be of value (for the formula

see p. 253). Later, transplants may grow aerobically. Growth is not usual with every attempt, so inoculation of a number of tubes is advisable. Surface colonies are pasty but of variable consistency and configuration. There is usually considerable pigment in the surrounding medium. Cultures of Actinomyces bovis almost always die quickly.

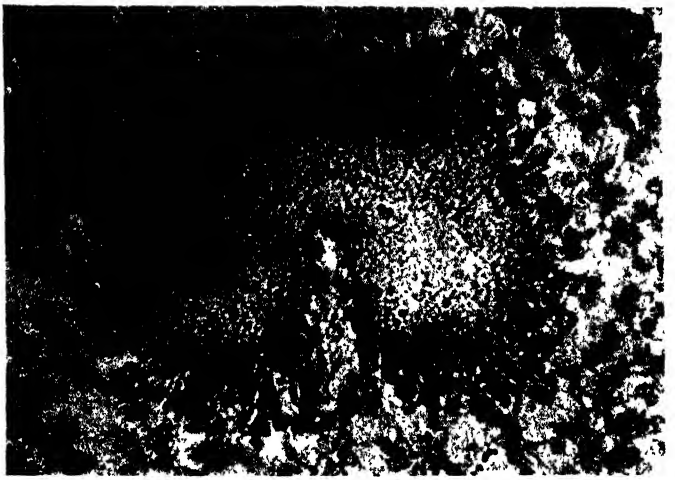

FIG. 92. Granule of Actinomyces present in tissue removed from a patient with maduromycosis. (*Courtesy of Wilbert Sachs.*)

(d) CULTURE MOUNT.—Interlacing hyphae are present without any characteristic spore forms.

(e) FILTERED ULTRAVIOLET RAYS.—The appearance is not distinctive.

(f) ANIMAL INOCULATION.—When cultural material is inoculated into animals an infection develops in only about 50 per cent. The infection is usually of minor importance and tends to heal spontaneously. This is interesting in view of the fact that the disease is most likely identical in animals and in human beings.

(g) DIFFERENTIAL DIAGNOSIS.—In the early stage of infection or when the disease is untreated, it is usually easy to demonstrate a typical granule. Secondary infection may mask the true nature. Culturing is difficult, and when no results are apparent from the direct mount or from attempts to culture, animal inoculation should be undertaken. (See also the following sections on S. schencki, B. dermatitidis and C. immitis.)

21. SPOROTRICHUM SCHENCKI

The chief, if not the only, cause of sporotrichosis in this country is probably a frequent saprophyte on many kinds of vegetation.

(a) IMMUNE REACTIONS.—The agglutination reaction is considered reliable by most observers. However, du Toit found that agglutination is produced by the serum of normal individuals. The intracutaneous test is of value, and a positive reaction is almost always present in patients with sporotrichosis.

(b) COLLECTION OF MATERIAL.—The organism is present in spore form in pus. If the lesion is not ulcerated, the pus may be withdrawn with a large caliber (no. 19) needle attached to a syringe. If ulceration has occurred, fresh pus from under the overhanging edges should be secured by gentle pressure and removed with a medicine dropper or a wire loop. Some of the pus may be dropped on slides for direct examination, but it is more important to transfer material to the surface of agar for cultures. This is done by streaking the drop of pus across the surface of the agar by means of repeated slashes with a sterile scalpel.

(c) MICROSCOPIC FEATURES.—The organism is seldom seen in fresh preparations. Lawless described a stain by which he was able to demonstrate the spores in fresh pus. One observes no mycelium but only cigar-shaped cells (Benham). It should again be mentioned that disappointment or error may follow if total reliance is placed on this procedure.

(d) CULTURAL CHARACTERISTICS.—The organism grows well in most laboratory mediums at room temperature and is readily identified.

On dextrose agar, after five to seven days, there develops a moist growth the size of a pinpoint, with a fine fringe. This slowly increases and in two weeks is about 2.5 cm. in diameter and is usually jet black. The surface is moist, and the central portion shows irregular convolutions. The border may be smooth at first but later becomes ridged. The color is gradually lost, becoming successively brown, tan and cream-colored in repeated subcultures. The color may be partially restored by adding yeast to the culture medium and incubating at 10 C. In old colonies, white excrescences appear on the surface. The young growth has a rubbery consistency tending to friability with increasing age.

(e) CULTURE MOUNT.—In the young colony, the mycelium is profuse, fine and branching. Fewer hyphae are observed in the older colonies. Pear-shaped conidia are present at irregular intervals along the course of the mycelium and may also appear as terminal triads and tetrads. Single spores may also be seen attached directly to the sides of the hyphae. The groups of spores are attached by short stalks (conidiophores). The spores vary in color with age and are apparently responsible for the color of the colony. Salvin considers S. schencki to be one of the more pleomorphic of the pathogenic fungi. On special mediums he was able to recognize at least four phases of development: yeastlike with single buds; yeastlike with multiple buds; "abortive-hyphal," and mycelial.

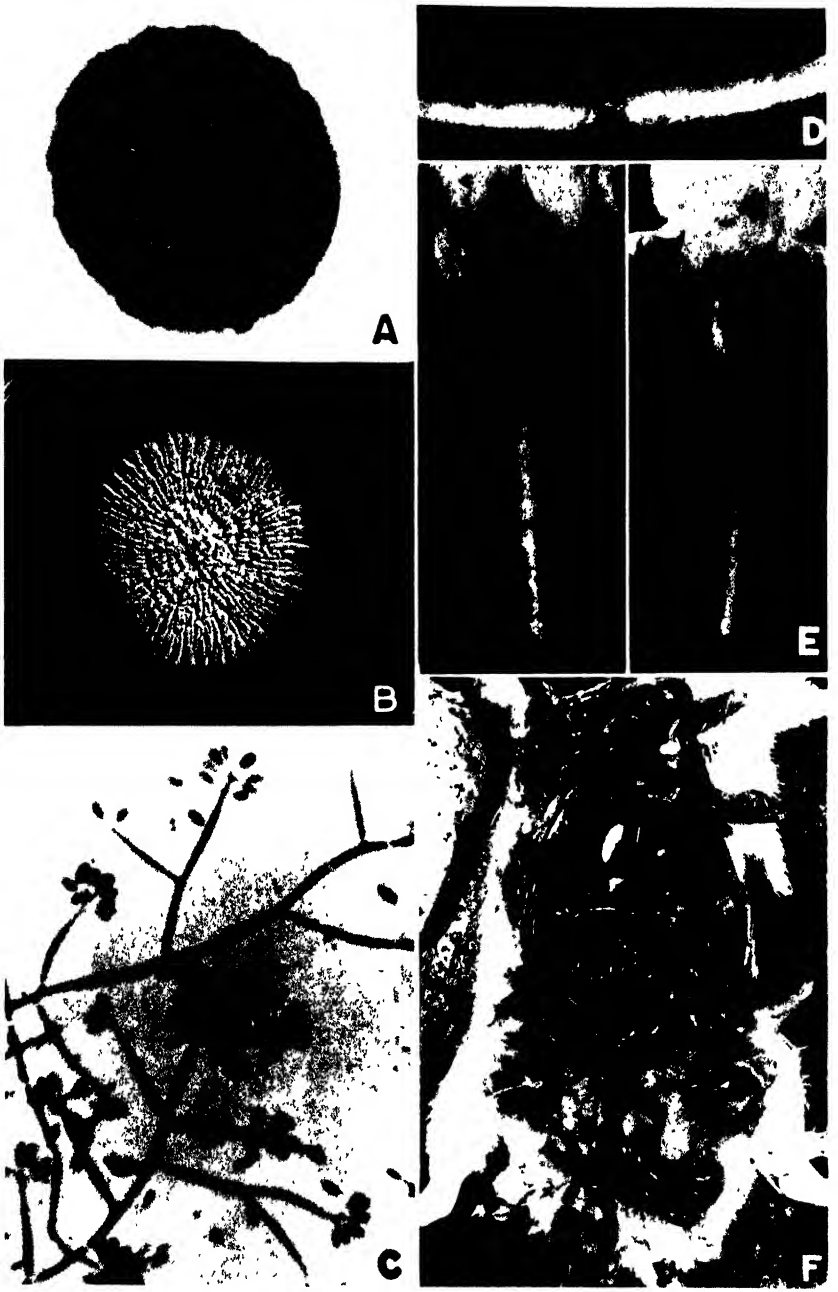

FIG. 93. Sporotrichum schencki. *A*, freshly isolated strain after four weeks; the jet black color is typical. *B*, colony with repeated subculture after 18 months; note loss of pigment. *C*, slide culture, showing clusters of spores borne at the tips of short stalks; × 500. *D*, ulcer in tail of rat at site of local injection of suspension of S. schencki. *E*, swollen testes and ulcerated tail of rat following inoculation. *F*, autopsy of rat following infection. All organs were normal except testes, which were heavily infected.

(f) FILTERED ULTRAVIOLET RAYS.—No change in the appearance is to be noted.

(g) ANIMAL INOCULATION.—Most laboratory animals are susceptible. The white rat is usually employed as particularly vulnerable. The testes of this animal usually become involved in the systemic infection.

(h) DIFFERENTIAL DIAGNOSIS.—The lack of results from a direct mount should make one suspect the presence of this fungus and practically rules out actinomycosis. The culture usually develops rapidly at room temperature and grows out characteristically. The clusters of ovoid spores borne at the ends of short side branches make the diagnosis certain. Blastomyces dermatitidis and C. immitis may usually be seen in a direct mount. On culture both the latter micro-organisms produce white filamentous growths. Both lack the groups of spores characteristic of S. schenckii. In case of doubt, animal inoculation will be helpful in obtaining a pure strain.

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22. BLASTOMYCES DERMATITIDIS

Castellani, Spring, Benham and others have shown that yeastlike fungi other than B. dermatitidis may cause granulomas resembling blastomycosis. Blastomyces dermatitidis, however, is probably the organism chiefly concerned in Gilchrist's disease and is to be searched for when blastomycosis is suspected. The etiologic and clinical features of this disease have been given on pages 197 to 203. Material from the newer lesions is preferable for examination.

(a) IMMUNOLOGIC REACTIONS.—Martin and Smith found that the majority of patients with blastomycosis react strongly to a heat-killed vaccine made from the yeastlike form of B. dermatitidis. A positive reaction is considered specific, although cross-sensitization has been reported with histoplasmin and occasionally with other antigens.

Martin found that the complement fixation test is specific. The antigen is made from the growth which develops on blood agar.

(b) MICROSCOPIC FEATURES.—When pus or sputum is obtained, a fresh preparation may be made by placing a drop of either material on a clean slide and covering it with a cover slip. The use of potassium hydroxide is not necessary unless the material is scanty. Budding thick-walled round or oval granular cells may be seen. If the suspected organisms do not show budding, the cover slip may be rimmed with petrolatum. After 24 to 48

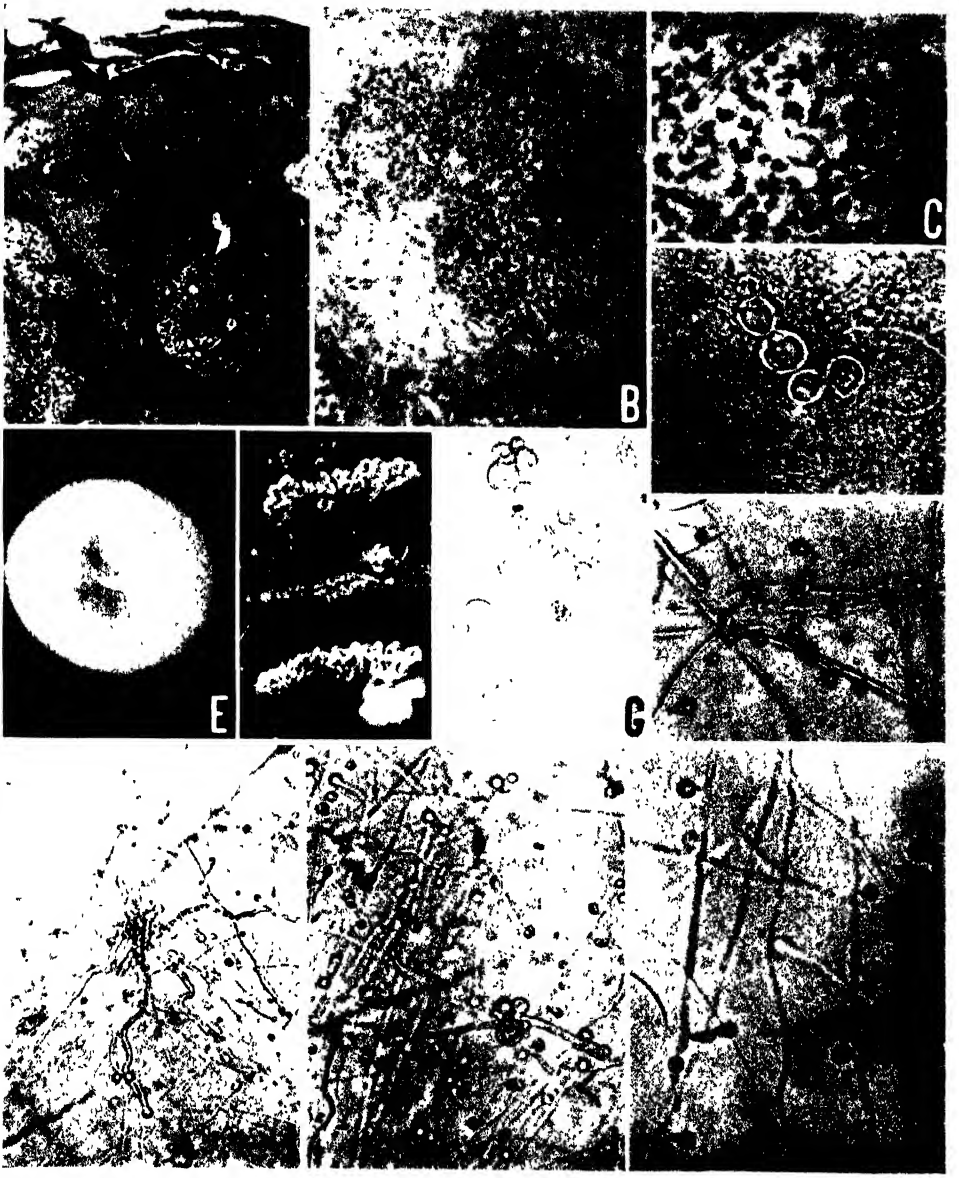

FIG. 94. Blastomyces dermatitidis. *A*, histologic section, shows granulomatous changes with multiple abscesses; × 35. *B* shows pus, mainly composed of polymorphonuclear leukocytes; × 150. *C*, the same section, shows the budding micro-organism; × 430. *D*, direct mount of pus, shows double-contoured budding cells. *E*, filamentous colony seen after three weeks, when growth develops on maltose agar at room temperature. *F*, colonies grown on blood agar at 37 C.; these are moist, brown and limited in size; × 1.8. *G*, mount from colony grown on blood agar at 37 C. after one week, showing double-contoured cells with budding; × 430. *H*, *I*, *J* and *K*, hanging-drop preparations from a colony growing at room temperature. With this temperature there is early germination of the capsulated form, with typical filaments; × 280, × 150, × 280 and × 555, respectively.

hours of such incubation at room temperature, budding may be noted. The organisms are from 8 to 20 microns or more in diameter. When a stained histologic section is examined, the budding organism may be noted in giant cells or in the granulation tissue.

(c) CULTURAL CHARACTERISTICS.—According to Martin and Smith, both dextrose agar and blood agar should be used in the attempt to culture this fungus. The dextrose agar is left at room temperature, and the blood agar is incubated at 37 C.

The colonies which develop on the incubated blood agar are small, compact and shiny. On dextrose agar the colonies are at first smooth and grayish but soon become filamentous and white, with a central umbo. A peripheral moist yeastlike zone is usually present. The organism grows moderately fast and in two or three weeks has developed to a good size. On blood agar, the subsurface growth is much greater. The yeastlike form may be maintained for long periods by being subcultured on blood agar and kept in the refrigerator. With age, the growths become brown and the surface may crack.

(d) CULTURE MOUNT.—Material from (yeastlike) colonies grown on blood agar reveals budding cells (blastospores) and occasional short rods with approximately the diameter of the other cells (Martin and Smith). Material from colonies grown on the dextrose agar shows mycelium with lateral conidia and large round cells (chlamydospores). Racquet mycelium may also be noted.

(e) FILTERED ULTRAVIOLET RAYS.—The appearance is not changed in young or in old colonies. No fluorescence is noted.

(f) ANIMAL INOCULATION.—According to Spring, the mouse is most susceptible, the rat is less so, and it is difficult to infect rabbits and guinea-pigs. The gonads are most vulnerable and are the usual site of inoculation. Generalization of the infection, even in mice, does not always occur; death should not be expected. The formation of abscesses may be considered a "take." Using an intravenous technic, Heilman was able to produce a uniform and rapidly fatal infection in mice. The time of death was directly related to the number of organisms administered. Death was due to embolic pneumonia.

(g) DIFFERENTIAL DIAGNOSIS.—If the budding micro-organism is observed in a direct preparation, the diagnosis may be made with certainty. There is a single bud in contradistinction to the multiple buds of P. brasiliensis. Actinomycosis is ruled out by the absence of granules in the pus. In C. immitis there is a variation in the size of the cells, budding is not present, and endospores may be present. Again, animal inoculation may be valuable in case of doubt.

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23. HISTOPLASMA CAPSULATUM

This fungus is the cause of histoplasmosis. Conant believes that it belongs among the Moniliaceae.

(a) IMMUNOLOGIC REACTIONS.—Sterile broth filtrates (histoplasmin) are said to elicit both tuberculin-like (delayed) and immediate responses in infected individuals. Cross-sensitization with blastomycin and coccidioidin has been reported.

(b) MICROSCOPIC FEATURES.—The specimen may be blood, urine, sputum or aspirated material from a lymph node, the sternum or the spleen. The material should be mounted both unstained and stained by Giemsa's method. The micro-organisms appear as round or oval yeastlike cells, usually budding. They may be present in endothelial leukocytes. A pseudocapsule is detectable. The cells measure 2 to 4 microns in diameter. A large vacuole and a large granule may be visualized. The oil immersion lens should be used.

(c) CULTURAL CHARACTERISTICS.—There are two cultural forms, depending on the technical method used. When cultivated on dextrose agar and incubated at room temperature, the colony is brown, glabrous, has an irregular surface and grows slowly. With age it takes on a white cottony appearance, particularly if the medium becomes dry. With some difficulty, the micro-organism may become pasty and moist when cultivated on sealed blood agar tubes at 37 C.

(d) CULTURE MOUNT.—Material taken from the glabrous and white cottony growths shows septate, branching hyphae. A characteristic finding is large, "thick-walled chlamydospores with a tuberculate sculpturing of the outer wall" (Conant). These chlamydospores are best demonstrated in specimens removed from mucoid growths which have developed on sealed blood agar tubes at 37 C.

(e) FILTERED ULTRAVIOLET RAYS.—No characteristic fluorescence is present.

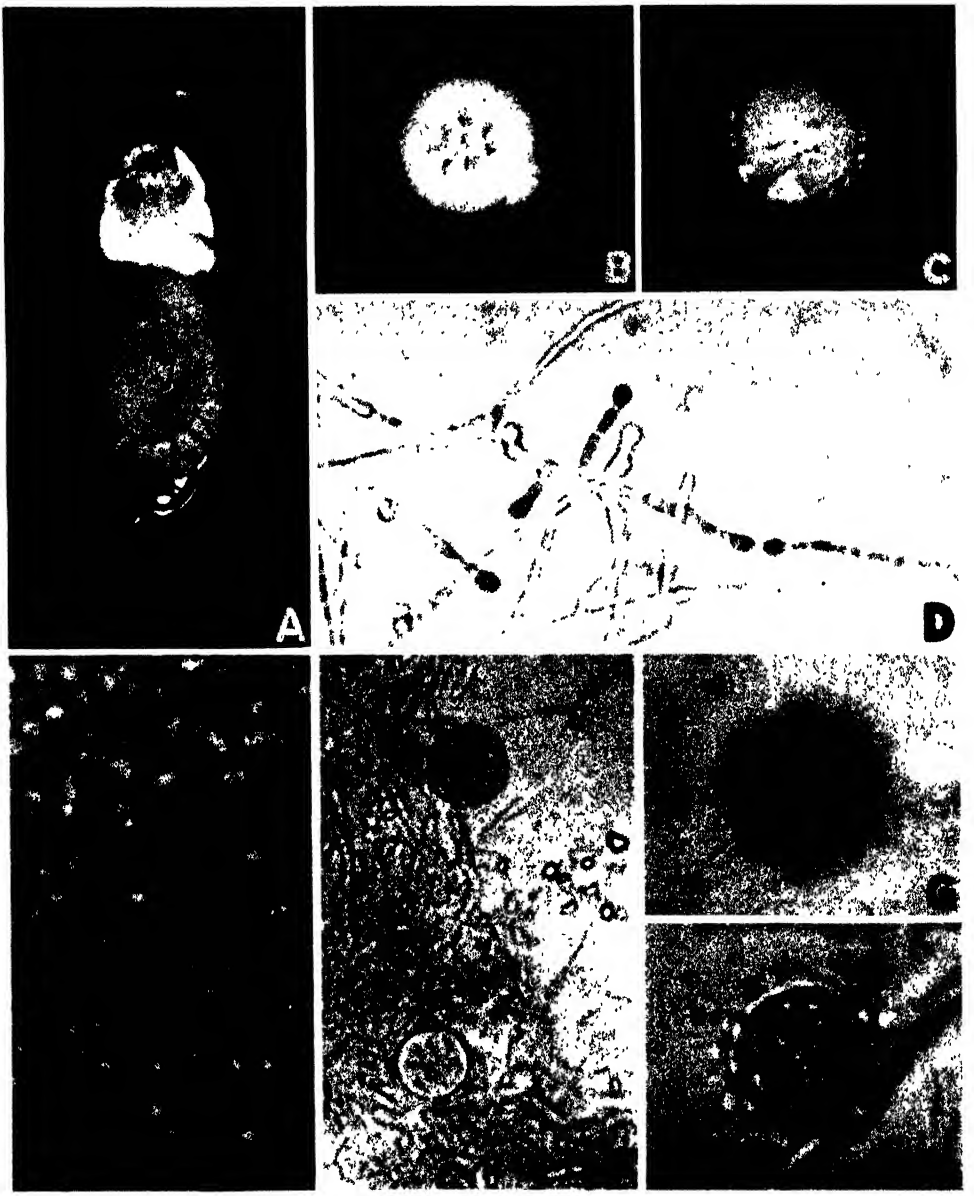

FIG. 95. Histoplasma capsulatum. *A*, subcultures on a 10 per cent blood dextrose agar slant at 37 C. after one month; growth is dull red, elevated and compactly duveteuse. The upper part of the colony, where the agar is thin, becomes fluffy and white. *B* and *C*, growths at one month on dextrose agar, the former enriched with 10 per cent whole blood. *D*, mount from dextrose broth culture at 37 C. showing terminal, lateral and intercalary chlamydospores; × 670. *E*, budding growth from yeastlike forms growing on sealed blood agar at 37 C.; × 1530. *F*, *G* and *H*, spiny and smooth-walled chlamydospores from colony on sealed blood agar at 37 C.; × 670, × 1530 and × 1530, respectively. (*Specimens, courtesy of M. E. Pinkerton, and A. C. Service and A. J. Donnelly.*)

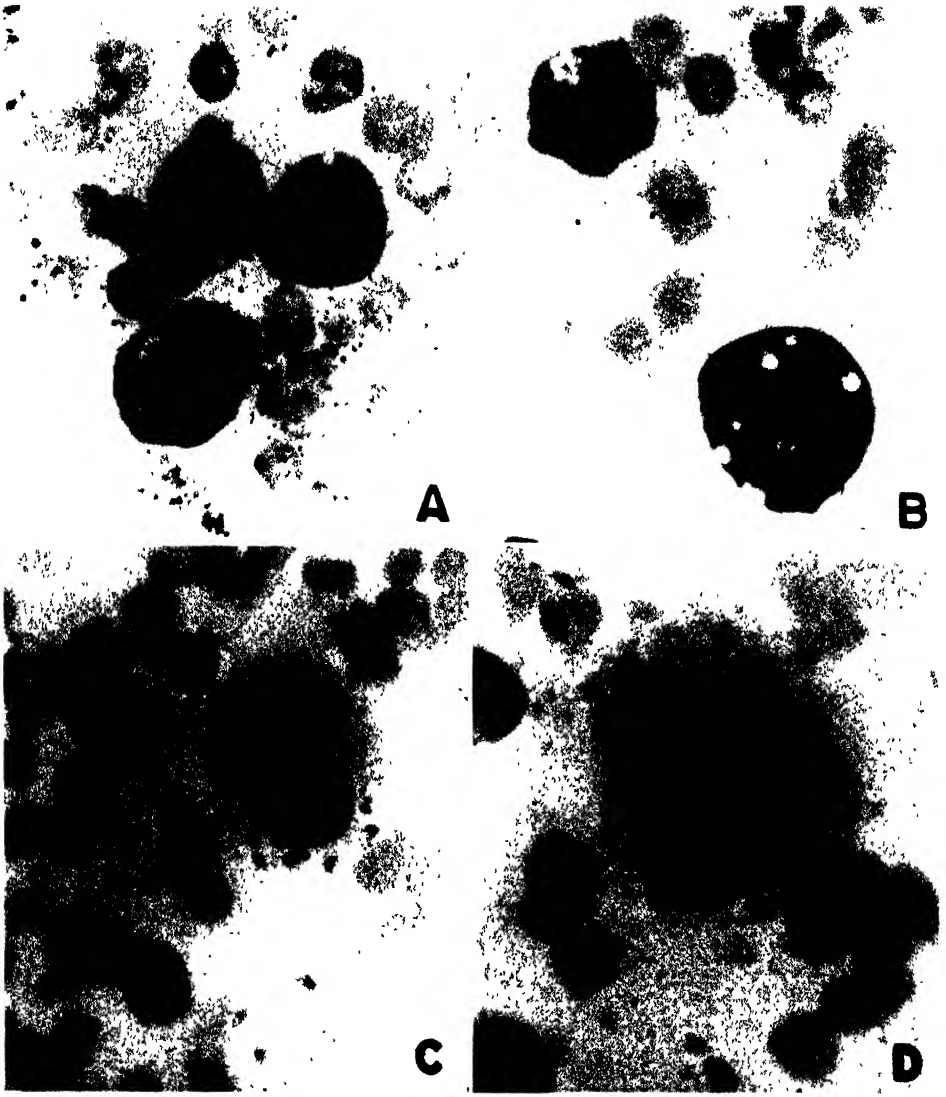

FIG. 96. Histoplasma capsulatum and Leishmania donovani. These two micro-organisms have been confused. *A* and *B*, Histoplasma capsulatum in bone marrow; × 1000 and × 1500. *C* and *D*, Leishmania donovani in spleen pulp; × 1000 and × 1500. (*Courtesy of Claude E. Forkner.*)

(f) ANIMAL INOCULATION.—Mice, rats, guinea-pigs and dogs develop fatal generalized infections when a suspension of the fungus is injected intraperitoneally. Monkeys are similarly susceptible when given intravenous injections (Howell).

(g) DIFFERENTIAL DIAGNOSIS.—When blood or other materials are examined, the intracellular oval or round yeastlike organism is characteristic. The cultural growth on dextrose agar is similar to B. dermatitidis. However, a culture mount will demonstrate the typical chlamydospores which will differentiate the two organisms.

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24. COCCIDIOIDES IMMITIS

There is general agreement that this organism is solely responsible for the disease coccidioidomycosis, as seen in this country.

(a) IMMUNE REACTION.—Dickson and others have held that the cutaneous reaction to coccidioidin is specific.

(b) COLLECTION OF MATERIAL.—Care must be taken that accidental infection of laboratory workers does not occur. The chief danger appears to be that spores from an old culture may be inhaled. Laboratory workers should wear masks while handling this micro-organism. The person obtaining a specimen from a patient should wear rubber gloves, although infection from man to man is unknown. As with other fungous diseases, material from a fresh lesion is preferable, and avoidance of grossly contaminated areas is to be desired.

(c) MICROSCOPIC FEATURES.—The micro-organism is to be found in free pus and in histologic sections. It consists of a sphere with a double-contoured capsule (ascus?) and is from 5 to 60 or more microns in diameter. Within the organism are from six to 20 round bodies (endospores, ascospores?). Rupture of the capsule results in dissemination of these spores and accounts for the sometimes rapid spread of the disease to areas remote from the primary focus. It is not usually necessary to stain the pus in order to demonstrate the micro-organism. As in demonstrating the ray fungus, a cover slip is dropped over a drop of pus on a clean slide and immediately examined. If the specimen is sputum or spinal fluid, the material may be concentrated by centrifugation and then examined.

(d) CULTURAL CHARACTERISTICS.—The material is streaked on the sur-

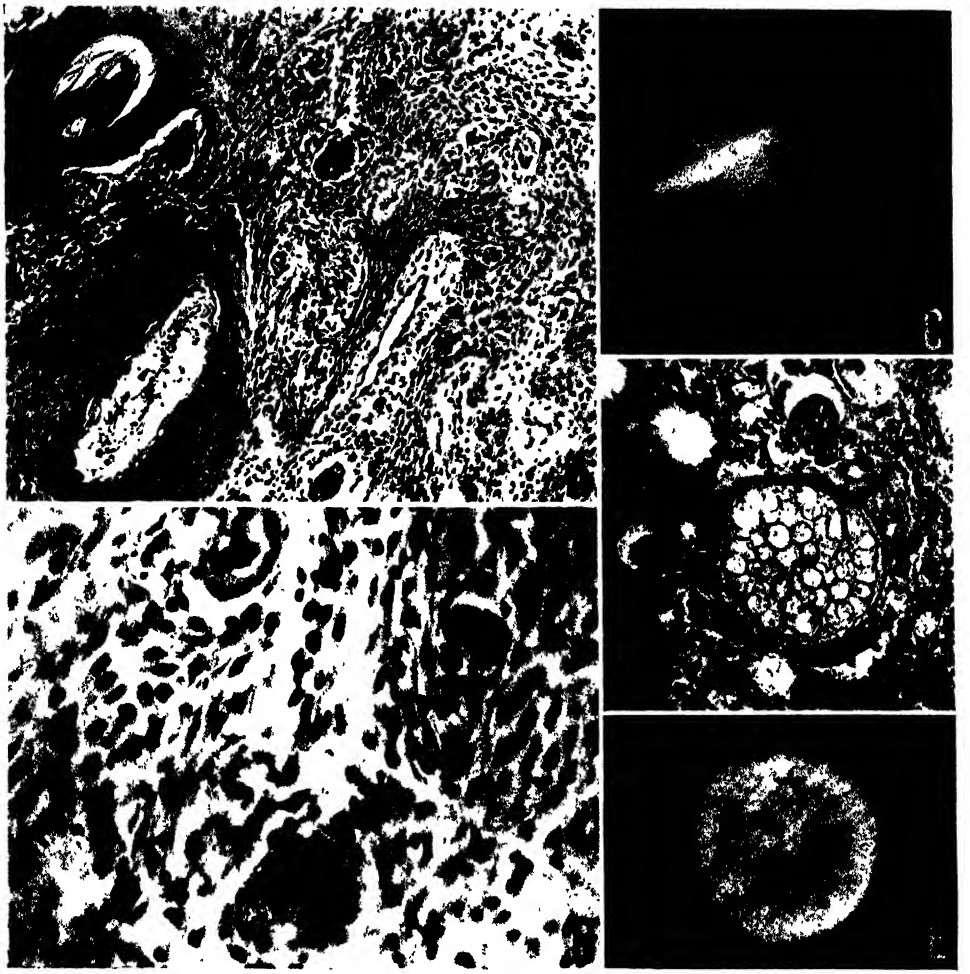

FIG. 97. Coccidioides immitis. *A*, section of a lesion of granuloma coccidioides, showing granulation tissue. Several parasites are present in the giant cells. *B*, high power view of *A*, showing giant cells and the type of cellular response. (*A and B, courtesy of Howard Morrow, H. E. Miller and L. R. Taussig.*) In *C*, rupture of the cell has liberated endospores. (*Courtesy of Leslie Smith.*) *D*, high power view, showing closely packed spores within the membrane. *E*, colony after three weeks.

face of dextrose agar and incubated at room temperature. Growth on this or on other common laboratory mediums is usually not difficult to accomplish. Within a few days a moist area appears. A creamy-white fluff soon covers the area, and growth is moderately rapid. The colony becomes brownish with age.

(e) CULTURE MOUNT.—There is a profuse growth of coarse mycelium (not observed in fresh preparations from the tissues). Coccidioides immitis is definitely septate, even in early colonies. Arthrospores and chlamydospores are to be observed. Identification of the organism in its cultural form can be made with certainty only by animal inoculation.

(f) FILTERED ULTRAVIOLET RAYS.—The appearance is unknown.

(g) ANIMAL INOCULATION.—Nearly all laboratory animals are susceptible. The guinea-pig is usually used. This animal is not nearly so susceptible to B. dermatitidis, the organism usually to be distinguished from C. immitis.

(h) DIFFERENTIAL DIAGNOSIS.—In human beings the organism should be differentiated from B. dermatitidis, P. brasiliensis, Rhinosporidium, Lycopodium and amebic cysts. In C. immitis the wall is thick, and endospores will be observed. In B. dermatitidis the wall is not so thick, and there is budding. In P. brasiliensis there are no endospores in the tissues, but the organism appears as budding cells in clusters. Animal inoculation is also more difficult to attain than with C. immitis. Rhinosporidium forms endospores in large numbers which are discharged through a definite opening; no cultural growth has yet been observed. Lycopodium spores resemble dusting powder, and amebic cysts may be confused.

25. PARACOCCIDIOIDES BRASILIENSIS

This is the cause of granuloma paracoccidioides, a rare disease endemic in South America. It has probably not been recognized elsewhere.

(a) CLINICAL CHARACTERISTICS.—The cutaneous lesions resemble those of granuloma coccidioides or of blastomycosis. The initial lesions are seen around the mouth, there is marked adenopathy, and if generalization occurs the intestines may be affected. These points clinically distinguish granuloma paracoccidioides from the other two diseases.

(b) MICROSCOPIC FEATURES.—The organism appears in tissue as a round cell, with multiple small buds (in blastomycosis, only one bud develops). No round form containing endospores is noted in tissue (in contrast to C. immitis).

(c) CULTURAL CHARACTERISTICS.—Growth is slow. At 37 C. on blood agar, the colony is small, cream-colored, yeastlike, compact and sharply demar-

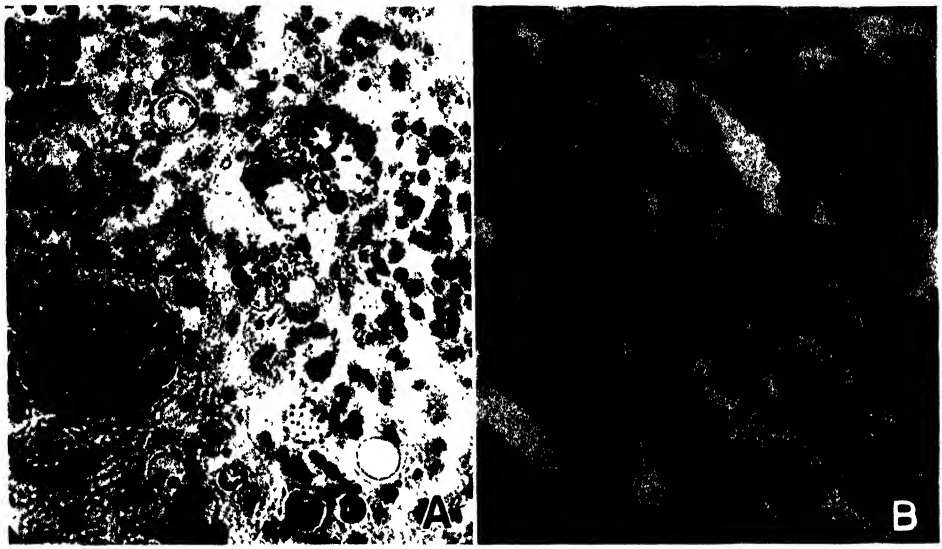

FIG. 98. Paracoccidioides (brasiliensis). *A*, different phases of life cycle; × 800. *B*, parasite in tissue; × 1000. (*Courtesy of Floriano de Almeida, São Paulo, Brazil.*)

cated. The surface is powdery and honeycombed. At room temperature, white cottony growths slowly develop, becoming brown with age.

(d) CULTURE MOUNT.—Multiple budding cells will be noted in material removed from the colony grown on blood agar at 37 C. Mycelium, chlamydospores and round cells containing endospores may be found in mounts made from the growth at room temperature.

(e) ANIMAL INOCULATION.—In rats small lesions develop. Conant and Howell were able to infect mice intraperitoneally and guinea-pigs intratesticularly.

(f) DIFFERENTIAL DIAGNOSIS.—In tissue, the multiple budding cell is characteristic. The culture may simulate that of B. dermatitidis.

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26. TORULA HISTOLYTICA (CRYPTOCOCCUS HOMINIS)

This is the cause of torulosis (European blastomycosis).

(a) CLINICAL CHARACTERISTICS.—The organism has a predilection for nerve tissue. Headache, lassitude and other symptoms of involvement of the central nervous system may be present. The spinal fluid is usually under pressure. Cutaneous lesions and lesions in other organs (particularly the lungs) may precede the meningitis.

(b) IMMUNOLOGIC REACTIONS.—Agglutination reactions are usually absent (Benham). Extracts of the organism are said to elicit specific cutaneous reactions in patients harboring the infection.

(c) MICROSCOPIC FEATURES.—In centrifuged specimens of spinal fluid the organism may be seen as budding cells of various sizes (5 to 20 microns). A wet India ink preparation shows the wide mucinoid envelope (capsule). In tissue a capsule may also be noted.

(d) CULTURAL CHARACTERISTICS.—On dextrose agar, at room temperature, the growth is moist and cream-colored, later becoming yellow and then brown. The surface is usually smooth. The colonies may grow slowly on primary culture and more rapidly after subculture.

(e) CULTURE MOUNT.—No mycelium and no ascospores will be noted. The cells are round or oval, and budding is commonly noted. If a preparation is made in India ink (as recommended by Weidman and Freeman), the capsule surrounding the cell will then be clearly observed.

(f) FILTERED ULTRAVIOLET RAYS.—No change in color and no fluorescence are to be noted.

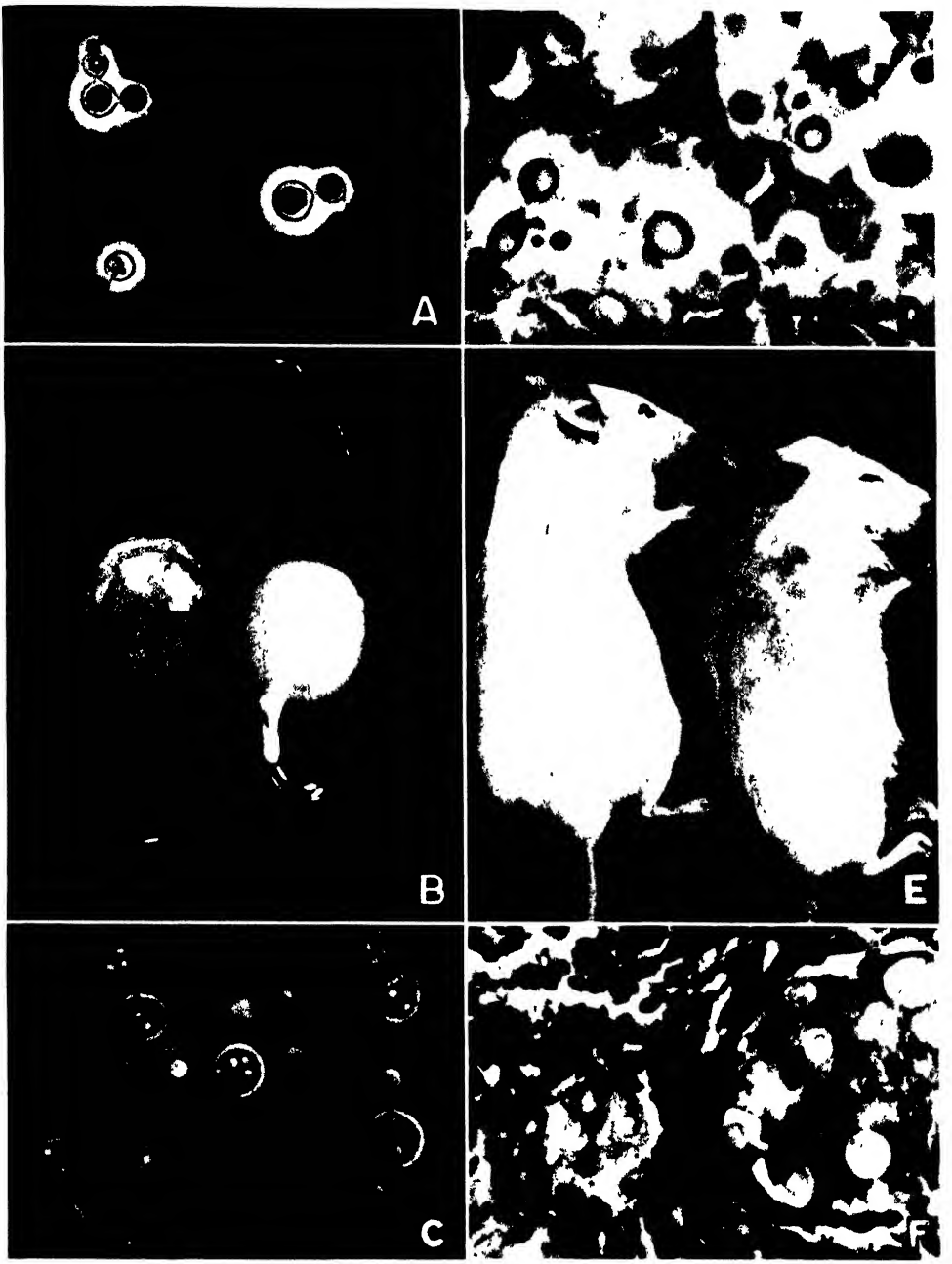

FIG. 99. Torula histolytica (Cryptococcus hominis). *A*, budding capsulated organism in spinal fluid, mounted in India ink. *B*, wet, pasty colonies grown on maltose and dextrose agar at 20 C. *C*, culture mount, showing budding forms and outline of capsule. (*Courtesy of James Herbert Mitchell.*) *D*, section of human brain, showing various sizes of budding organism surrounded by clear envelope. *E*, infected mouse with enlargement of skull, with normal mouse for comparison. *F*, section of guinea-pig liver, showing budding cells; × 480.

(g) ANIMAL INOCULATION.—Mice and rats are the most susceptible and rabbits and guinea-pigs less so (Benham). The infective material, diluted in saline, should be injected intraperitoneally. The animal usually dies within two to four weeks.

(h) DIFFERENTIAL DIAGNOSIS.—In M. albicans mycelium develops, particularly on corn meal agar. The cell of B. dermatitidis is larger and lacks the thick mucinoid envelope of T. histolytica. The cells of C. immitis contain endospores. Other, nonpathogenic cryptococci are not pathogenic to mice.

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27. RHINOSPORIDIUM SEEBERI

This is the cause of rhinosporidiosis, a rare fungous disease with a predilection for the anterior nares. The fungus was first described by Ashworth in 1923.

(a) MICROSCOPIC FEATURES.—The material for examination may consist of freshly prepared slides from nasal secretion or tissue or stained slides from a biopsy section. The micro-organism is large (up to 250 microns in diameter), thick-walled and spherical. There are many endospores which are eventually discharged. In a histologic slide the fungus is in the cutis.

(b) CULTURAL CHARACTERISTICS.—This fungus is reputed not to grow on ordinary laboratory mediums. We have had no experience.

(c) ANIMAL INOCULATION.—No laboratory animal is susceptible.

(d) DIFFERENTIAL DIAGNOSIS.—When the site of a polypoid growth of the nose is the source, R. seeberi should be suspected. There may be a superficial resemblance to C. immitis, but the large size of R. seeberi should alone be sufficient to distinguish the two fungi.

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CHAPTER XXXIII

Other Pathogenic Fungi

NUMEROUS other species of fungi undoubtedly have a capacity for parasitic invasion. Only a brief description of their characteristics will be given, since in our experience they are mainly laboratory specimens. We believe that they will be rarely isolated in this country. More detailed descriptions may be found in one of the texts mentioned in the list of reference books, page 357.

1. MICROSPORUM EQUINUM

This fungus is pathogenic for animals, particularly the horse. Infection of human beings is found chiefly in those who have contact with horses. The clinical appearance of the infection simulates that of an infection caused by M. lanosum. On culture a white downy growth with radial grooves results. Fuseaux are less numerous than with M. lanosum.

2. ACHORION QUINCKEANUM

Infection with this fungus (the cause of mouse favus) is evidenced clinically by inflammatory lesions. Scutula may form in mice but not in human beings. On culture the growth is white and downy, with concentric foldings and radial grooves. Microconidia, fuseaux and nodular organs may be seen in the culture mount.

3. ACHORION GALLINAE

This fungus (the cause of chicken favus) is probably not pathogenic for man. The surface configuration and microscopic appearance are similar to those of A. quinckeanum. A strawberry-red color is distinctive.

fuseaux and microconidia similar to those of M. lanosum.

4. MICROSPORUM SIMIAE

This fungus (a parasite of monkeys) was isolated by us in a single instance from the scalp of a child with tinea capitis. There was a history of contact with a monkey. The diseased hair fluoresced like hair infected by other Microspora, and the microscopic appearance also was similar. On culture the growth was fluffy and white and development was slower than that of M. lanosum. Radial grooves were present. The culture mount showed

5. TRICHOPHYTON ACUMINATUM (ENDOTHRIX)

The growth is similar to that of T. crateriforme, the only difference, in some instances, being the direction of development. Trichophyton acuminatum grows upward. The surface is usually powdery; the color varies from cream to brown; the center is sharply elevated, and radial striations are common.

6. TRICHOPHYTON CEREBRIFORME (ENDOTHRIX)

The clinical appearance of infected lesions, the features revealed by direct examination and the culture mount are similar to those of T. crateriforme. The central break which forms a depression in the cultural growth, so typical of T. crateriforme, is not present.

7. TRICHOPHYTON ROSACEUM (ENDOTHRIX)

It has been suggested that this may be a highly tinted strain of T. purpureum. It is described, however, as an endothrix. It has been isolated from the beard, nails and glabrous skin. The cultural growth is downy, there is a central umbo, and radial grooves are usually present. The pale rose color gradually suffuses through the colony. The culture medium becomes "gooseberry-violet." Emmons has drawn attention to the confusion which may occur owing to its similarity to a saprophytic Fusarium.

8. ACTINOMYCES TENUIS

This is the reputed cause of lepothrix. Delicate, nonseptate hyphae may be demonstrated in potash mounts. The cultural growth is sparse, wet and pasty.

9. TRICHOSPORUM (PIEDRAIA) HORTAI

A cause of tinea nodosa, this fungus may be demonstrated in potash preparation of a severed node. There are numerous hyphae which are branched and septate. Asci containing two to eight spores may be demonstrated. On culture, the growth is slow, the color black and glabrous. Chlamydospores and occasional asci may be present.

10. TRICHOSPORUM GIGANTEUM

The reputed cause of "white" tinea nodosa, this fungus reveals a mass of hyphae and occasional budding cells in potash mounts. The cultures are moist, light yellow and nonfilamentous.

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CHAPTER XXXIV

Fungi Probably Pathogenic

THE list of fungi which are probably pathogenic is too long, and a discussion of all the fungi in it would become too involved for this text. There is evidence that the fungi to be mentioned are capable of causing disease in human beings.

1. ASPERGILLUS FUMIGATUS

This mold has been isolated by many different observers from diseased tissue (see the section on otomycosis, Chapter IX, pp. 168 f., and on aspergillosis, Chapter X, pp. 219 f.). Its chief role is probably that of a secondary invader; in that capacity it may be responsible for the continuance of an infection originally caused by some other micro-organism. On dextrose agar the growth is filamentous and greenish. The conidial head is green, the stalks are smooth, and the vesicle is flask-shaped; the sterigmata occur in one series and round conidia in narrow columns.

2. PITYROSPORUM OVALE

During recent years many studies have been made of the possible pathogenic role of P. ovale, a fungus originally described by Malassez and also known as the bottle bacillus of Unna. The investigation of its pathogenicity has been hindered by the difficulty of obtaining a cultural growth. Success in growing the organism was reported by MacLeod and Dowling in 1928. Previously Unna, Engman, Castellani, Templeton, Acton and Panja, and Ota and Huang reported occasional success in attempts to cultivate the fungus. Templeton employed a preparation containing beer wort agar. Moore used wort agar (Difco), a medium made especially for the cultivation of yeasts; subcultures were usually made after three or four days. Moore reported success in culturing P. ovale in approximately 10 per cent of

cases and attributed his failure in the remainder to a considerable concomitant growth of common air-borne fungi. It was possible to inoculate other mediums successfully from a vigorous primary growth. Benham, Emmons and others have also been occasionally successful in obtaining a cultural growth of P. ovale.

In a report on the possible role of P. ovale as the cause of seborrheic dermatitis, Moore, Kile, Engman and Engman found that inoculation of the cultures of an organism which they believed to be P. ovale in human subjects and in animals frequently resulted in the development of a "dermatitis of erythema or brown scaliness," the histologic picture of which resembled that of seborrheic eczema. They stated that the reproduction of a dermatitis, as reported by MacLeod and Dowling, was the most convincing evidence in favor of the etiologic importance of a microbe. In a prior report Moore expressed doubt that the organism isolated by MacLeod and Dowling was P. ovale. It seems, therefore, that rigid control tests both as to subjects and as to the inoculated material are essential in order to determine pathogenicity by inoculation experiments. Moore, Kile, Engman and Engman reported that cutaneous tests on 18 patients with different extracts prepared from the cultural growth of P. ovale resulted in a number of positive reactions. These reactions were manifested by the development of an area of erythema at the site of injection, and in a few instances a scaly red dermatitis appeared. No mention was made of control tests. In a second and more complete study, Kile and Engman inoculated P. ovale and produced a scaly condition on human scalps from which P. ovale was again recovered. Control tests with two other fungi failed to produce comparable inoculation results.

In a survey of the scalps of 100 patients, MacKee, Lewis, Spence and Hopper made an arbitrary clinical differentiation into five groups based on clinical features common to each group. Pityrosporum ovale was frequently noted in all groups, being present on 70 per cent of normal scalps and on 66 per cent of the scalps on which there was a concomitant skin disease. In the majority of examinations, it was found that the concentration of the organism was higher on scalps with dandruff than on normal scalps. In a second series of patients it was noted that P. ovale was also a common inhabitant of the skin, more frequently found in scrapings from the surface of the nose than in material manually expressed from the nose. There is still divided opinion among investigators regarding the pathogenicity of P. ovale. Many feel that the work of Engman and his collaborators is decisive and that there is as much, if not more, proof of a causal relationship between P. ovale and dandruff as between M. furfur and tinea versicolor.

(a) MICROSCOPIC FEATURES.—In a search for the micro-organism the chief

reliance is to be placed on a direct mount. We use a technic of staining with methylene blue (see the section on the direct mount, Chapter XVIII, pp. 235 ff.). The organism is noted as an ovoid or spherical cell with or without budding. The flask-shaped cell is characteristic. The diameter varies from 2 to 10 microns.

(b) CULTURAL CHARACTERISTICS.—The medium which Moore found most favorable for primary isolation is wort agar, which, as already mentioned, is a Difco product with a pH of 4.8. He reported success in approximately 10 per cent of cases. The following medium may be used for subculture when it is desired to keep the growth alive:

Technical maltose, and Technical dextrose	aa	2 per cent
Peptone		1 per cent
Agar		1.8 per cent
Distilled water		q.s.

Wheat germ oil or butter should then be added, since Benham has shown that P. ovale requires a fatty environment. We studied three strains. The growth was first noted on the fourth day after inoculation. The rate of growth was slow to moderate, the ultimate size being limited. The color was tan. The cultures were compact, smooth and glistening, with no bubbles.

According to Moore, the colony measures approximately 2 cm. in diameter after 40 days. The culture is pulvinate, with radiating ridges to the periphery, a rough surface and a few small excrescences. The color is dull and varies from light ochraceous salmon to pinkish buff.

(c) CULTURE MOUNT.—The cells vary from 3 to 15 microns in diameter, most of them being from 4 to 5 microns. There are many budding cells resembling bottles or gourds. The large cells appear to be thickly encapsulated or to have a thick gelatinous structure due to the medium. Several cells show more than one bud. The budding cells appear to be small or divided. Elongated forms had a mean length and width of 5 and 4 microns, respectively.

(d) ANIMAL INOCULATION.—Moore's cultural growth has been inoculated into the skin of rabbits, with a resultant scaly rash which disappeared spontaneously.

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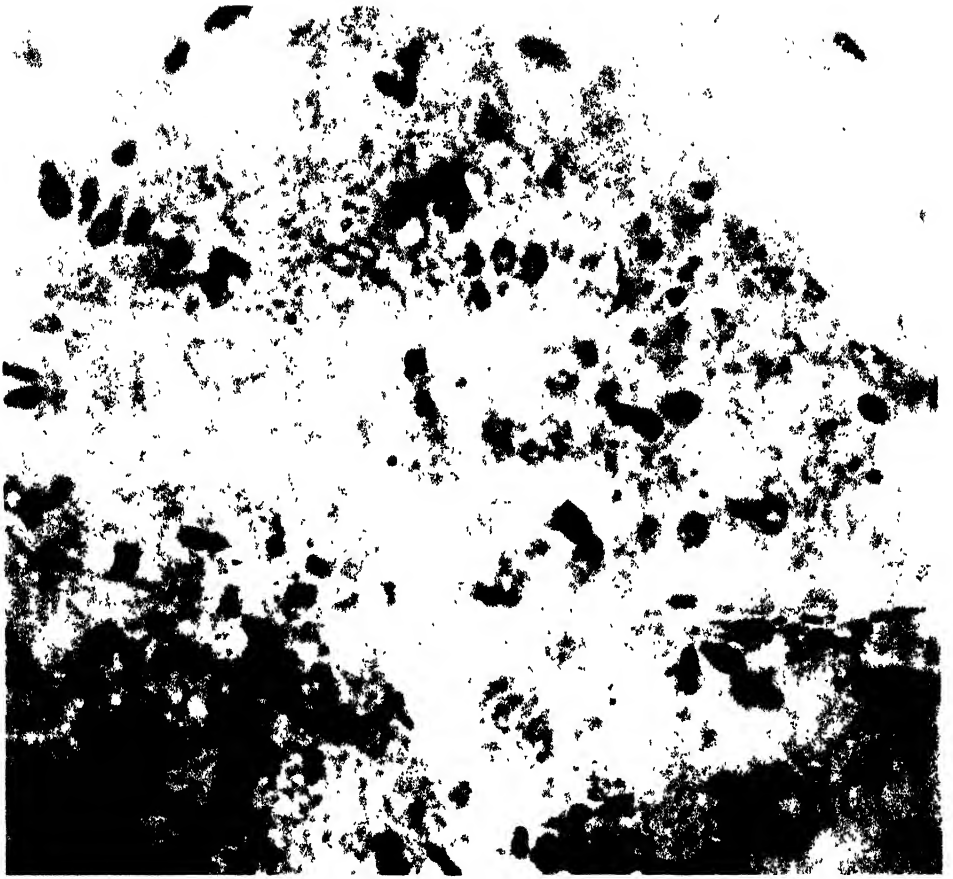

FIG. 100. Pityrosporum ovale. There are variously sized cells, including dumbbell- and flask-shaped forms; × 1925.

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CHAPTER XXXV

Fungi Questionably Pathogenic

1. SAPROPHYTES ASSUMING PATHOGENICITY

UNDER this heading might be placed instances of infection in which fungi are secondary invaders and it is difficult to determine whether their presence is more than incidental. It is our opinion that much harm has been done and the progress of medical mycology has been delayed because of the confusion due to the numerous case reports of supposed mycoses. After a critical analysis of many of these reports, one concludes that proof was frequently insufficient. It is probably true, of course, that the difference between pathogenic and purely saprophytic existence is not great; factors of lowered resistance of the host or the development of a strain of increased virulence may account for a certain number of genuinely mycotic infections. It would probably be wise, however, to be skeptical regarding claims of pathogenicity of fungi of ordinarily nonpathogenic species unless more proof of their pathogenicity is offered than their mere occurrence in diseased tissue. Such tissue is suitable soil for growth and propagation of fungi, but in this they may fail to affect the normal tissues of the host. The ideal procedure would be reinoculation of the living organism into healthy human tissue; but this is not often possible, nor is it desirable in every case. Animal inoculation can never be as valuable a procedure, since the susceptibility to infection is not the same even in different species of animals and is not likely to be the same in animals as in human beings. Repeated isolation of a particular species of fungus, even if it is commonly saprophytic, is likely to impress the worker unduly, and the need for further proof is not considered necessary. It would be helpful if, when the diagnosis is based solely on the isolation of a fungus, the reporter would use a question mark in the title to indicate doubt as to the diagnosis.

In a case of deep nodular and ulcerating lesions from which Scopulariopsis brevicaulis (a saprophyte found on vegetable and other organic matter)

was isolated, Markley, Philpott and Weidman stated that although the micro-organism was not identified either in pus or in histologic section they believed it to be the cause of the disease because (1) there was reasonable exclusion of other etiologic factors, (2) granulomas were produced in experimental rats, (3) the parasite remained viable for 37 days in such animals, (4) the reports of others indicated pathogenicity of a similar strain and (5) the pus from which cultures were secured came from a closed lesion. There is no doubt that the evidence is strongly in favor of the conclusions drawn. Weidman had previously considered Scopulariopsis as capable of causing tinea unguium. We have obtained strains of Scopulariopsis on a number of occasions, frequently in repeated scrapings from the same patient, but when nails are undoubtedly invaded by fungi, this finding has, with one exception, been incidental. Usually Scopulariopsis was present superficially and the real pathogen was found in the deeper parts of the nail. In the one exception, repeated cultures at various depths of the nail continued to yield a species of Scopulariopsis. The partial evulsion, achieved as the result of taking specimens, resulted in cure.

In many cases reported in the last few years a species of Aspergillus has been considered of pathogenic titer. A critical analysis of many of the reports fails to reveal sufficient evidence to incriminate the mold as more than an incidental contaminant. In a case reported by Myers and Dunn, an ulcerated granulomatous lesion had been present on the back of the hand for two years. Only a staphylococcus was obtained on blood agar cultures. Roentgen therapy and moist boric acid packs were administered for six weeks without improvement. Then cultures on Sabouraud's medium yielded an Aspergillus. Cure was credited to the use of an ointment containing 1 per cent copper subacetate, although it would be more logical to assume that the roentgen rays (dosage not mentioned) administered while the diagnosis was still pyoderma were more than mildly contributory to the favorable result. This case was cited by Frank and Alton, who in turn reported in detail an extremely superficial infection, said to be due to Aspergillus niger in a postoperative skin dressing, which healed overnight after an application of iodine and alcohol. They had observed two similar cases previously. It is a question whether many saprophytes under the same condition would not have produced a similar picture. Frank and Alton stated that of 375 species of Aspergillus, 57 are pathogenic and 40 are pathogenic for human beings. The term pathogenic seems to be rather loosely interpreted by these authors. The reports cited could be multiplied many times; this is one reason why medical mycology has become confused. Careful attention to technic in removing material for culture will usually result in the elimination of surface contaminants.

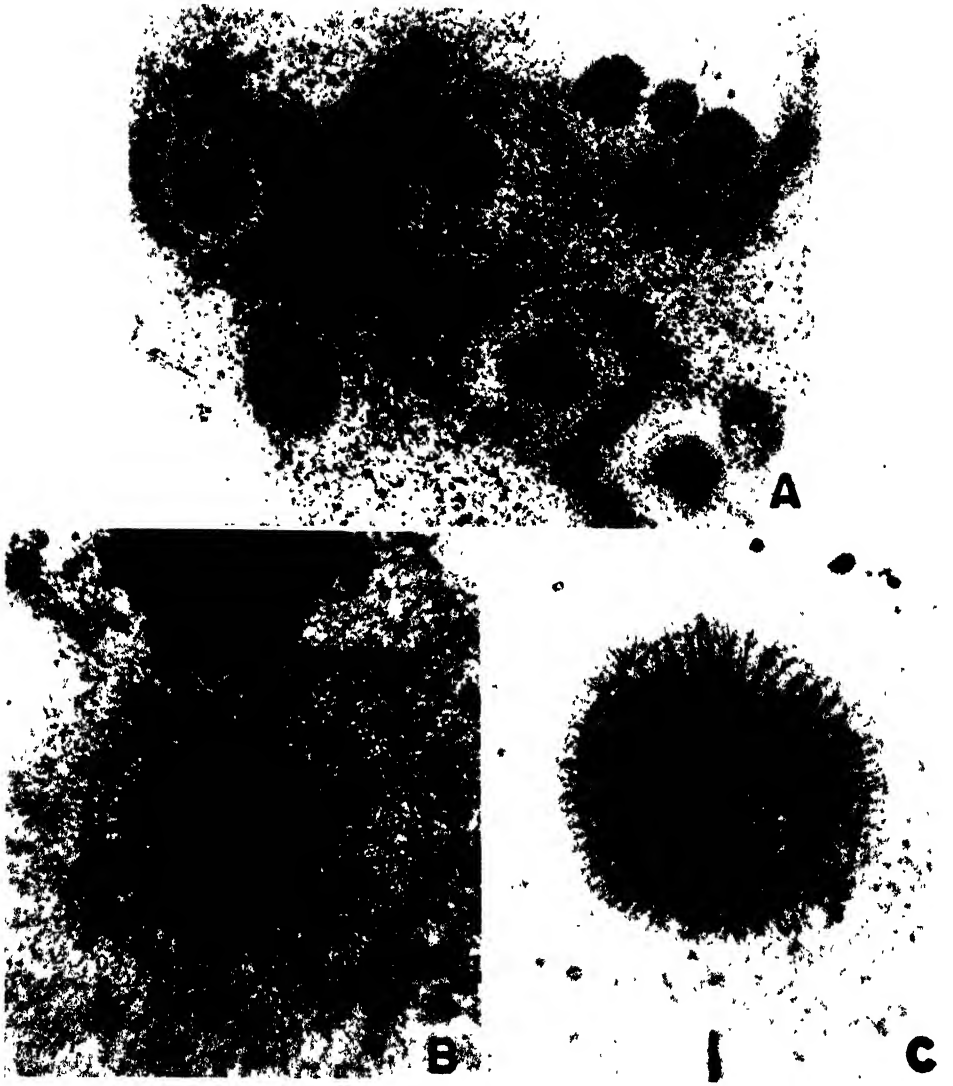

FIG. 101. Aspergillus niger present in profusion in scraping from acutely inflamed ear canal. The micro-organism was repeatedly cultured and no other cause could be found for the disorder. *A*, numerous heads of various ages with radiating structures bearing masses of spores; × 100. *B* and *C*, higher magnification to show structure of the head; × 220 and × 480.

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2. INADEQUATE AND CONFLICTING EVIDENCE

In a report on streptothrichosis, Kovnat and Mezei made the amazing statement that "sporotrichosis, streptotrichosis, nocardiosis, madura foot, pseudo-actinomycosis and other designations all cover the same pleomorphic organism." They reported a case of fatal pulmonary infection. Twenty-two days after the onset of the disease, fresh sputum treated with 10 per cent potassium hydroxide showed the presence of many brown granules which, crushed and examined microscopically, consisted of spores and mycelium with true branching, suggesting Streptothrix as the causative organism. The authors stated that "continued study of the sputum on plain smear and culture bore out the impression of a streptothrix infection." They recovered the same organism from pus of a subcutaneous lesion which subsequently developed and also noted a similar fungus in a pathologic specimen of a lesion resembling a sebaceous cyst which had been surgically removed before the onset of the fatal disease. Here the incomplete identification of the fungus leaves one in doubt as to whether the patient died of pneumonia, tuberculosis or a mycosis.

A case report invaluable in illustrating incomplete evidence and illogical reasoning is that of Hollingsworth. The patient was a man aged 65 who had on the back of one hand a nodular ulcerated lesion of 2½ years' duration. Several physicians had previously made a diagnosis of cancer. The patient stated that the lesion developed after injury with a thorn. Subsequently he had come in contact with a cow who had lumpy jaw. Cure resulted when a complete surgical excision was performed. Fungicidal remedies were also employed. The histologic report revealed a "well differentiated, early, squamous cell epithelioma, type 1, not highly malignant." No fungi were observed in the pathologic tissue. Material which at operation was thought to be a granule subsequently was found to consist mainly of keratinized cells. In one slide Hollingsworth thought he saw definite evidence of branching mycelium. The case was reported as an unusual example of actinomycosis. It may have been, but no evidence was presented to dispute the histologic evidence of epithelioma.

The cases here mentioned were not carefully selected but are representa-

tive of many reported in the medical literature. We do not wish to go on record as not believing that in many instances the disease reported was caused by a fungus of uncommon pathogenic propensity. Rather we wish to emphasize the difficulty of offering adequate proof short of the study of a series of patients, with mycologic, histologic and immunologic observations and, if possible, with experimental autoinoculation. When the diagnosis is in doubt or when an ordinary saprophyte is isolated, proof of pathogenicity is squarely the responsibility of the reporter. As we have stated, when sufficient evidence is lacking, the doubt as to the diagnosis should be indicated in the title by a question mark.

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CHAPTER XXXVI

Common Contaminants

THE organisms discussed in this chapter are frequently observed as contaminants on culture mediums. Their isolation, although accidental, may crowd out micro-organisms of pathogenic titer; this has been a source of confusion to the beginner and of annoyance to the more experienced.

The greatest trouble is experienced from contamination with molds. Bacteria grow poorly at room temperature, and yeastlike organisms grow so slowly that they may be readily discarded. Molds grow quickly, and the aerial mycelium is considerable. The inside of a culture tube may be literally covered with the growth within two or three days. The rapidity of development and the appearance of heavy pigment (green, brown, black) is frequently sufficient to indicate the nature of the mold. At times the growth is white, later turning to green, and unless the rate of growth is known some confusion may arise. If any doubt exists, a culture mount will soon reveal the diagnosis.

It has been mentioned that various observers have credited many of these fungi with having pathogenic propensities in isolated instances. We urge caution in this direction; unless experimental autoinoculation is performed it is usually best to question the diagnosis. Some reports of pathogenic strains of common saprophytes have already been discussed.

Because they are air-borne, molds may also be important in the pathogenesis of asthma. This is considered elsewhere.

Since in this text we are not primarily concerned with fungi of nonpathogenic propensities, the differentiation into species will be cursory. The description of the genera should be sufficient for identification.

1. ASPERGILLUS

The mycelium develops a stalk (conidiophore) which enlarges to form a knoblike projection (vesicle) on which regular finger-like processes

(sterigmata) are formed. Chains of spores (conidia) are seen to develop from the sterigmata. In certain species there is also seen a perithecium, or ascus, which contains spores (ascospores). Species of Aspergillus are chiefly identified by the color of the spores and special characteristics. Only a few of the common species of Aspergilli are discussed.

(a) ASPERGILLUS GLAUCUS.—This is one of the commonest contaminants. It has green conidia and yellow perithecia.

(b) ASPERGILLUS FUMIGATUS.—See Chapter XXXIV, "Fungi Probably Pathogenic."

(c) ASPERGILLUS NIGER.—This has brown or black conidia.

(d) ASPERGILLUS NIDULANS.—This has bright green conidia, branched sterigmata and pink perithecia.

(e) ASPERGILLUS FLAVUS.—This has yellowish-green conidia and a rough stalk.

(f) ASPERGILLUS CANDIDUS.—This is colorless.

2. PENICILLIUM

There is no enlargement of the conidiophore to form a vesicle. Instead, the sterigmata appear directly on the stalk. They have many variations. There may be only primary sterigmata from which chains of spores are formed, or the sterigmata may branch once or twice. Another variation is the development of aberrant sterigmata, which results in an asymmetrical appearance.

3. MUCOR

These organisms are commonly found as bread molds. The mycelium is abundant, coarse and nonseptate. The typical finding is a sporangium which is a black or brown rounded receptacle situated at a terminal portion of a hypha.

4. ALTERNARIA (MACROSPORIUM)

The multichambered pyriform spores are present in continuity with the vegetative hyphae. There may or may not be mycelium between the spores. The color of the spores may be dark olive, green or brown.

5. HORMODENDRUM

From the sterigma (stalk) arise spores, which are usually olive-green. They are formed from one another in chains, the youngest cell being at the

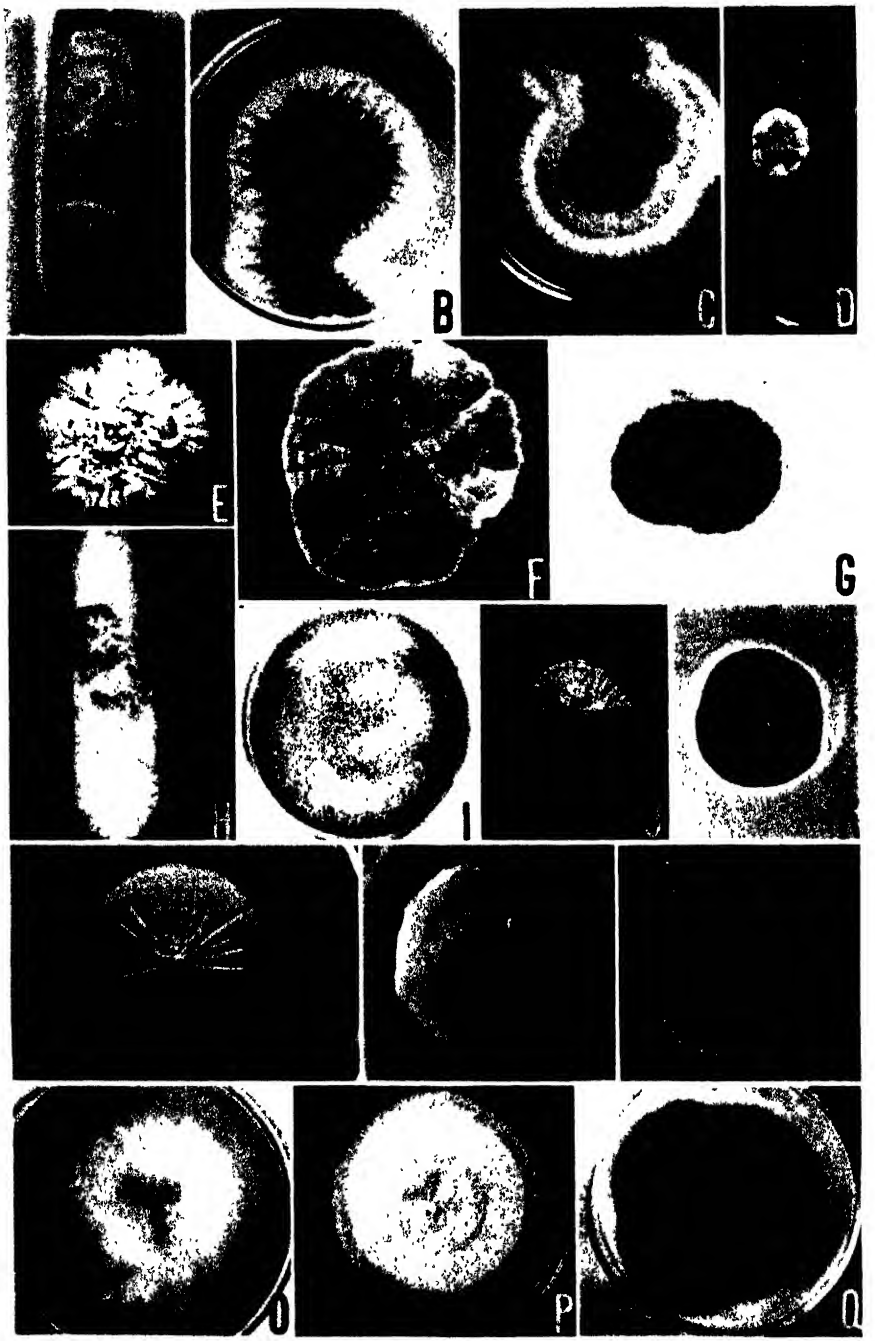

FIG. 102. Common contaminants. *A*, A. candidus. *B*, A. niger. *C*, A. flavus. *D*, Aspergillus of unknown species. *E*, Mycoderma. *F*, Scopulariopsis. *G*, Hormodendrum. *H*, Chaetomium. *I*, Rhizopus nigricans. *J*, Monilia krusei. *K*, Hormiscium. *L*, Monilia candida. *M*, Torula (pink, smooth). *N*, Torula (pink, rough). *O*, Fusarium. *P*, Trichothecium. *Q*, Alternaria.

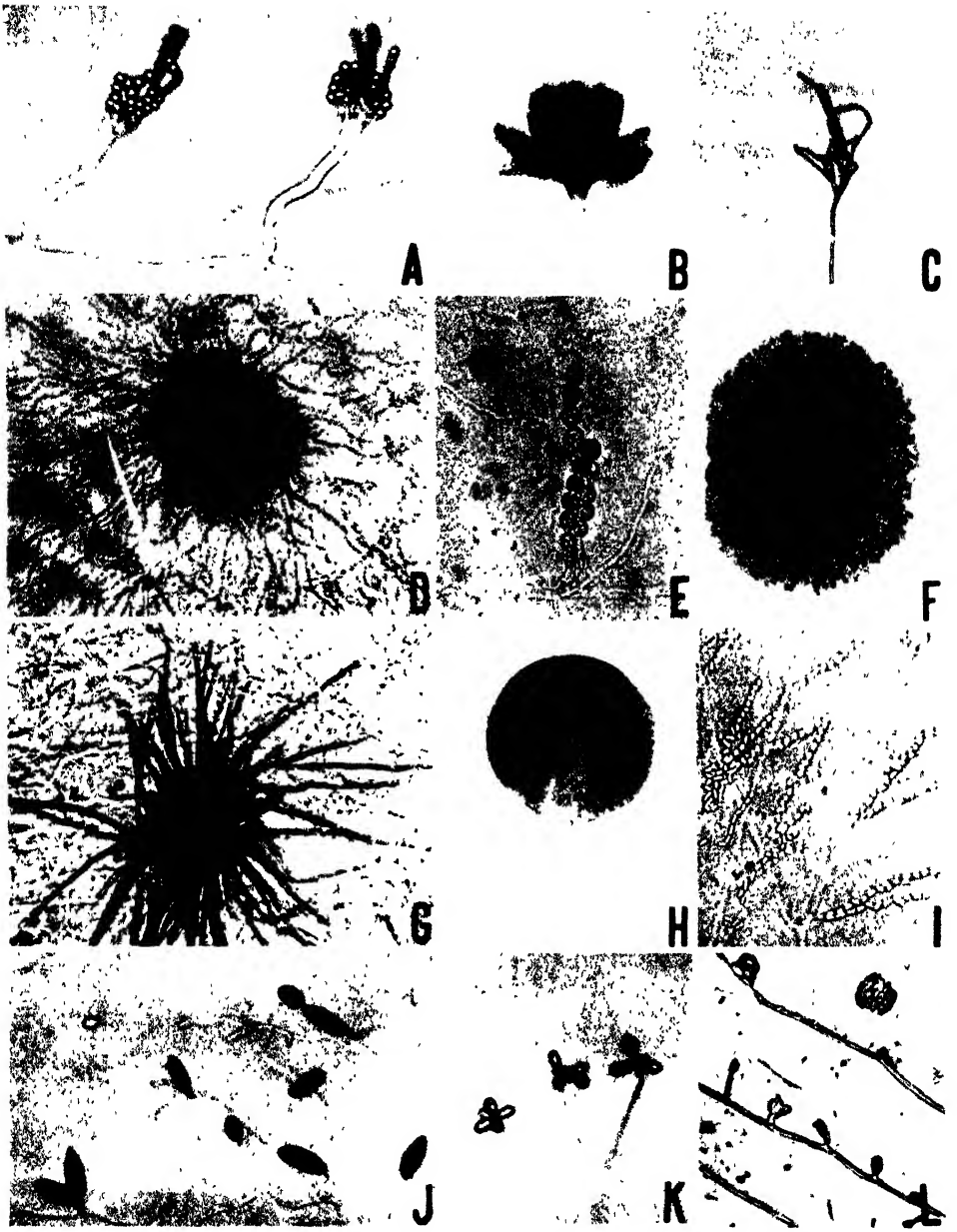

FIG. 103. Common contaminants. *A* and *B*, species of Aspergillus. *C*, Penicillium. *D*, perithecium of Aspergillus containing ascospores. *E*, Scopulariopsis. *F*, Hormodendrum. *G*, Chaetomium. *H*, R. nigricans. *I*, Mycoderma. *J*, Alternaria. *K*, Trichothecium. *L*, Fusarium.

end. On the contrary, with both Aspergillus and Penicillium the spores are formed from the sterigma, the youngest cell being nearest the stalk.

6. FUSARIUM

The sterigma is branched. Spores occur as spindle-shaped cells with indistinct cross-walls.

7. SCOPULARIOPSIS

The branching of the conidiophore is irregular. Spores appear in chains, are yellowish brown and have a spiny wall.

8. DEMATIUM

The hyphae are septate. Arising from them on lateral branches are chains of small black arthrospores.

9. MYCODERMA

The hyphae are septate. Arthrospores form.

10. TORULA (CRYPTOCOCCUS)

The surface of the colony may be smooth or rough. The color is often pink. The cells are thin-walled and show budding. There is no mycelium.

11. CHAETOMIUM

The spores are produced in a thick-walled spiny perithecium. They can be observed microscopically.

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