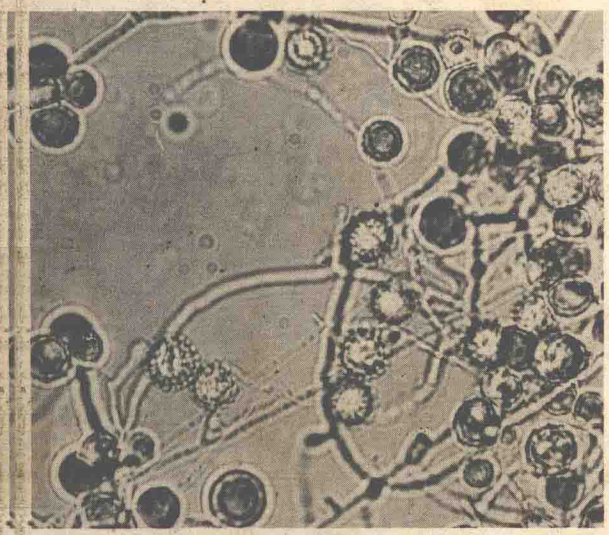
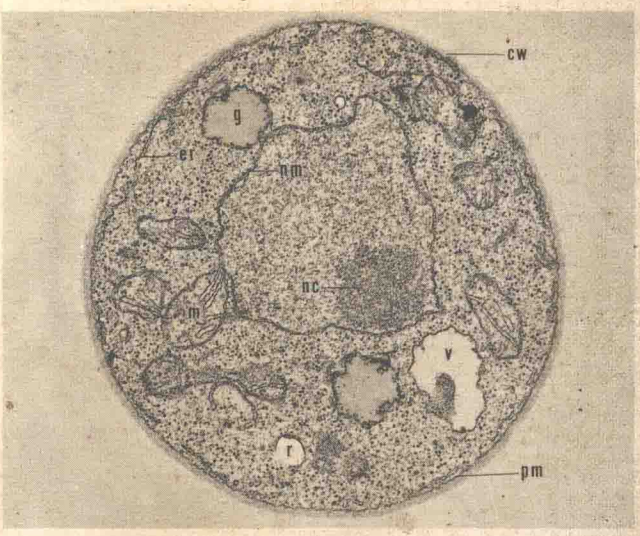
Chester W. Emmons
Chapman H. Binford
John P. Utz

MEDICAL MYCOLOGY





SECOND EDITION

CHESTER W. EMMONS, Ph.D.

Chief (Retired), Medical Mycology Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; Mycologist, Department of Dermatology, College of Physicians and Surgeons, New York, 1929–1934; Mycologist, Department of Dermatology, School of Tropical Medicine, San Juan, Puerto Rico, 1935; Professorial Lecturer, George Washington University School of Medicine, 1942–1966; Consultant in Mycology, Armed Forces Institute of Pathology, 1954–1966.

CHAPMAN H. BINFORD, A.B., M.D.

Medical Director, Leonard Wood Memorial Foundation; Medical Director (Retired), U. S. Public Health Service; Chief, Special Mycobacterial Diseases Branch, Armed Forces Institute of Pathology, Washington, D. C.

JOHN P. UTZ, M.D.

Professor of Medicine, Chairman, Division of Allergy and Infectious Diseases, Medical College of Virginia, Richmond, Virginia, 23219; Chief (Retired), Infectious Diseases Service, Laboratory of Clinical Investigations, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Medical Mycology

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Preface

The degree of acceptance of the first edition of *Medical Mycology*, the depletion of its second printing, and new developments in medical mycology since 1963 have prompted us to prepare this second edition of the book. The widespread use of antibacterial antibiotics, immunosuppressive drugs and drugs used in cancer therapy have resulted in a presumptive increase in mycoses. This probable increase, the limited success of antimycotic drugs, the toxicity of the one antibiotic now available and effective against disseminated mycoses, and more general use of effective diagnostic procedures have increased the interest in and relative importance of mycoses within the decade just past.

This revision of *Medical Mycology* has involved extensive changes and additions in the first four introductory chapters. The traditional assumption that fungi were derived from algae by loss of chlorophyll has been replaced by the more modern concept that fungi are not primitive plants, but were derived from some remote ancestral groups in the Protista. The subject of phylogeny is not explored in depth, but the reader is referred to sources of information. We again have attempted to relate medical mycology to general mycology, but this edition (like its predecessor) makes no pretense that it approaches the comprehensive review of fungi required in a textbook of mycology. The lists of literature references for these and other chapters have been extended, but we regretfully admit that we have inadvertently or by necessity omitted many important titles which would be useful to the reader. Ainsworth's estimate that 1200 to 1500 items appear annually in the world literature of medical mycology emphasizes the dependence of the student upon abstract journals.

We have adopted a few changes in terminology and nomenclature in this second edition, and the reasons for these are given at the appropriate places. For the most part, the nomenclature of fungi and of mycoses follows that of "Nomenclature of fungi pathogenic to man and animals," Memorandum No. 23 of the Medical Research Council of the United Kingdom, 1967.

Dr. Utz has replaced Chapters 6 and 7 on immunology, serology and therapy of the mycoses by more extended discussions of these important subjects, and he has revised the corresponding sections in the chapters on specific mycoses. Dr. D. J. Winslow has rewritten the section on pathology of the mycetomas, which he had contributed to the first edition. We are indebted to the McGraw-Hill Book Company for permission to use the material in Appendix III which was published previously by them in *Manual of Histologic and Staining Technics*, 1968.

Most of the photomicrographs of fungi were made by the senior author while he was at the National Institutes of Health. For the photographs of colonies of fungi we are indebted to the skills of artists in the Photographic Section, National Institutes of Health. Most of the photomicrographs which illustrate histopathology were obtained by Dr. Binford from the Photographic Division of AFIP. Dr. H. I. Lurie, now at the Medical College of Virginia, Richmond, supplied some of the material for illustrations of the histopathology of sporotrichosis from his extensive experience

with this mycosis in South Africa. As in the first edition, clinical illustrations for the dermatophytoses were supplied by Dr. P. H. Jacobs. Drs. D. Connor, M. Gordon, C. Hesseltine, A. Howell, M. S. R. Hutt, D. B. Jelliffe, L. Pine, P. Stockdale, B. Tynes, L. A. Weed and J. P. Wiersema supplied other illustrations, as credited in the legends, for both the first and second editions.

For permission to use additional new or previously published photographs in this edition we are gratefully indebted to Drs. G. Bras, C. H. Bridges, B. M. Clark, R. R. Davies, A. Dumont, M. R. Edwards, Lie-Kian-Joe, H. I. Lurie, F. D. Martinson, C. Piché, R. B. Powell, R. Renoirte, H. J. Shadomy, H. Spencer, J. Vandepitte, F. von Lichtenberg, P. O. Wakelin, A. O. Williams, and E. S. McDonough.

Phoenix, Arizona — Chester W. Emmons
Washington, D.C. — Chapman H. Binford
Richmond, Virginia — John P. Utz

Contents

Introduction

In 1835 Bassi observed that muscardine, a disease of the silkworm, was caused by a fungus. Shortly thereafter the mycotic etiologies of favus, of other types of ringworm and of thrush in man were recognized. Since these early discoveries in medical mycology, the parasitic relationships of certain fungi to plants, insects and animals have attracted the attention of many investigators. During the last 20 years of the nineteenth century Sabouraud began his monumental studies of the dermatophytes or ringworm fungi which culminated in 1910 in the publication of his classic, "Les Teignes." This period was notable also for the isolation in culture and the description and naming of such important pathogens as *Actinomyces bovis, Candida albicans, Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis* and *Sporothrix schenckii.*

Shortly after the turn of the century Darling first observed and carefully characterized histoplasmosis, Brumpt recognized the nature and importance of some of the mycetomas, and the allergic and immunologic studies of dermatophytoses by Bloch and his school gave further impetus to the study of mycotic infections of man and of their etiologic agents. During the ensuing 20 years chromomycosis was reported as an important but rare disease and the clinical importance and high fatality rates of paracoccidioidomycosis were recognized.

The diversity and thoroughness of these studies up to 1925 provided a broad foundation for the later development of Medical Mycology. Taxonomic errors and mistakes in interpretation may be found in many of these early papers, although some of the reported studies stand today as classics of careful research, meticulous observation and accurate interpretation. The errors were the inevitable attributes of a medical specialty in which newly discovered etiologic agents of disease were being studied without adequate techniques, background or basic information. Most of these early studies were made by dermatologists, internists or pathologists, often without the collaboration of a professional mycologist or with only casual consultation. *Coccidioides* and *Histoplasma* were described and named as protozoa prior to their isolation in culture and mycologic study. Generic and specific names (*e.g., Monilia, Blastomyces* and *Torula histolytica*) were selected erroneously in disregard or ignorance of prior use of such names for other fungi, or after erroneous interpretations of morphology or histopathology. Species names were multiplied unnecessarily because authors had not searched earlier mycological or medical literature adequately or because they did not evaluate properly the normal variation in morphology, size and pigmentation within a species.

Mycologists share with physicians responsibility for many errors of these types. Fungi pathogenic for man were regarded by many mycologists who might have been given an opportunity to study them, as aberrant and unimportant. Other mycologists recognized properly that these mycotic agents of disease presented grave hazards in mycology laboratories which lacked safety hoods and other equipment essential to safeguard students and other personnel. Even mycologists who have specialized in the study of

these pathogens have confused some systematic relationships and made many taxonomic errors. The taxonomy and nomenclature of some groups of fungi (such as the diverse but apparently closely related etiologic agents of chromomycosis) present such inherent difficulties that mycologists still disagree about them.

During the past three decades mycologists have accepted greater responsibility for the study of fungi of medical importance, and physicians have learned that mycoses are more frequent causes of morbidity and death than had been recognized previously. Together they have given more attention to the mycoses in differential diagnoses of disease, studied clinical variability in the mycoses, improved methods of detecting and identifying fungi found in tissue sections, and emphasized the necessity for isolation of fungi in culture. Collaboration between physician and mycologist has been placed upon a more substantial basis, to the benefit of both their sciences.

Medical mycology is an integral part of general mycology as well as an important specialty in medicine. Each major group of fungi includes species which are pathogenic or toxic for man. The pathogens are represented in some instances by groups of related species which are well adapted to invasion of mammalian tissues and are known mainly in this parasitic relationship, in other cases by fungi which cause disease only under unusual circumstances but are well known as saprobes in man's environment, and finally by toxic fungi which cause illness or death after ingestion. Fungi of a fourth group are important as allergens. The first two groups are invariably recognized as being within the realm of medical mycology and the latter two should be included in this field.

In this book, for brevity, the term "pathogenic fungus" refers to pathogenicity for man and animals. For the plant pathologist, however, the unqualified term refers to pathogens of plants. It should be noted in this connection that the number of fungi physiologically adapted to either localized or systemic parasitism of plants far exceeds the number recognized as pathogens of man.

There are more than 200,000 specific names of fungi in mycological literature. Many of these are synonyms of earlier names. Many others have been applied to fungi which differ from a valid species by only minor variations in size, color, form, or in host relationship or geographic distribution. Depending upon his evaluation of minor variations, a mycologist may estimate the total number of valid species of fungi at 50,000 or 500,000. Among fungi and actinomycetes there are at least 20 species which cause systemic and potentially fatal disease; 35 which cause less severe systemic disease or severe localized cutaneous, subcutaneous or lymphatic infections; and 45 which cause superficial infections of the skin, its associated keratinized tissues or the mucosa. Fungi of the latter group penetrate only rarely into deeper tissues. Fungi which capture amoebae, nematodes and insects by means of highly specialized trap-like structures, and those which parasitize by less spectacular methods such microfauna of air and soil as insects and their larvae, number several hundred. Except for brief recognition at appropriate places in the text, the pathogens of insects and the microfauna of soil are beyond the scope of this book. Allergenic molds and toxic mushrooms perhaps equal in numbers the pathogens of man, animals and insects.

In addition to the 100 or more species of fungi which are generally recognized as pathogens of man, it is firmly established that under unusual cir-

cumstances of abnormal susceptibility of the patient, or of the traumatic implantation of the fungus, other fungi are capable of causing lesions. These circumstances may include a debilitated or diabetic condition of the host; a concurrent disease such as leukemia; hypersusceptibility after prolonged treatment of a patient with corticosteroids, immunosuppressive drugs or antibiotics; abrasion of an avascular and immunologically deficient tissue such as the cornea; or repeated exposure of the feet of unshod workmen in tropical areas to penetrating thorns. Some of the fungi which invade tissue under these conditions may be listed as provisional pathogens until the study of additional cases reveals more clearly the frequency and the limits of clinical variability of the mycoses which they cause.

The essential reasons for the pathogenicity of these fungi can be expressed at the present time in only general terms of tolerance of the fungi to temperatures of 35 to 37° C, possession of enzyme systems which permit them to parasitize animal tissues, and circumstances which provide an effective exposure of the host to spores of the fungi. Some fungi, such as *Histoplasma capsulatum*, ordinarily cause a mild or even asymptomatic infection. Such fungi, however, can cause a severe or fatal disease if exposure is by inhalation of many spores or if other modifying factors intervene. These factors are not fully known, but in some cases they include impairment of the individual's normal defenses by a concurrent condition such as Hodgkin's disease.

With few exceptions the systemic, lymphatic, and subcutaneous mycoses are caused by fungi which are essentially free-living saprobes in nature. These mycoses are not contagious, and infection in man and animals follows inhalation or traumatic implantation of the fungi from their normal saprobic habitats in decaying vegetation, humus, bird, or animal excreta, soil or soil enriched by bird or animal excreta. Production of systemic diseases by fungi which are essentially saprobes, and only by accident pathogens of man, is the rule rather than the exception in medical mycology.

The fungi which cause systemic and subcutaneous mycoses have been called "opportunistic fungi" to emphasize the aspect of a normally saprobic fungus which can suddenly become parasitic and pathogenic when it is introduced by inhalation or traumatic implantation into the human body. The term can be criticized for its anthropomorphic implications. It has been used also to designate fungi which cause disease only in a patient with a concurrent disease which increases his susceptibility, or in one whose innate immunity has been otherwise impaired. This use of the term for a secondary disease is not easily defended because fungi such as *Histoplasma capsulatum* and *Coccidioides immitis* are primary pathogens in normal persons. They are "opportunistic" according to the first definition but not according to the second. To call them "opportunistic" only in those cases in which the mycosis is secondary to another disease is inconsistent and implies a dichotomy among the agents of mycoses that, in most cases, cannot be clearly defined.

Recognition of the saprobic nature of fungi which cause mycoses, of their predilection for specific types of enriched soil or organic debris, and of the ecologic (but not parasitic) relationships which some of them bear to specific animals or birds are essential to an understanding of the epidemiology of the mycoses. Associations between *Coccidioides* and rodent burrows in an arid soil of high salinity, between *Histoplasma* and excreta of chickens, feral birds or bats, and between *Cryptococcus* and pigeon dung are examples, now

fully documented, of such ecologic associations. The associations cited are neither invariable nor essential, but they are so frequent that, since their discoveries, the epidemiologist investigating sources of infection in a patient should first enquire whether he has had such an exposure.

During the past 25 years the literature of medical and veterinary mycology has increased at a rate estimated to be about equal to that of scientific literature in general. Ainsworth (Sabouraudia, *5*, 81–86, 1966) analyzed and discussed "The pattern of medical and veterinary mycological information," as reflected in the Review of Medical and Veterinary Mycology and its antecedent abstract journals published by the Commonwealth Mycological Institute. He noted that since 1943 the increase in number of titles abstracted annually in the *Review* is linear, and it has doubled over a 12-year period. Including papers not reviewed in this abstract journal, he estimated the annual output at 1200 to 1500 items, about a quarter of which were in veterinary mycology. In 1964–1965, 952 abstracts were drawn from 351 different serial publications, illustrating wide scatter among a few mycologic journals and a large number of medical and veterinary journals. Volume 4 of the *Review of Medical and Veterinary Mycology* listed 229 pathogenic fungi and actinomycetes and 40 toxic fungi. This number of fungi is more than twice the number we include in this book, which is limited by our lack of personal experience with some of the rare or unique mycoses, by our concepts of synonymy and etiologic importance, and by omission of several fungi that are important only in veterinary medicine as pathogens or toxic molds. We have not attempted to write a comprehensive compilation of all fungi reported to be pathogenic.

Reports on dermatophytes represent the largest subject group in the literature of medical mycology. Many of these report the geographic distribution of dermatophytes isolated either from dermatophytosis or from soil. They indicate continued, renewed, or recently awakened interest in these ubiquitous fungi in many parts of the world. Next in order of frequency are papers on candidiasis, mycotoxicoses and toxic mushrooms, and histoplasmosis.

Some formerly assumed geographic limits on distribution of pathogenic fungi, now are recognized as fallacious. Exotic mycoses introduced by an immigrant or a traveler have been recognized, but some of the breaches of geographic barriers cannot be explained on either this basis or the accidental importation of an exotic fungus in commerce, *e.g.*, as a contaminant on packing materials. *Histoplasma capsulatum* is a preeminent example of a fungus which can exist undetected in a geographic area. "North American" blastomycosis now is known to be endemic in Africa, and some "African" dermatophytes have made unexplained appearances in the United States. Do some of the "new species" of dermatophytes represent mutations which appear spontaneously, now and then, and independently in different parts of the world? Reports of new mycoses and of newly discovered endemic areas for well-known mycoses add important items to our knowledge, while at the same time, they indicate the imperfect and developing state of medical mycology.

Chapter 1

Role of Fungi in the Economy of Nature

NATURAL HABITATS

Degradation of Organic Compounds. Fungi share with animals and most bacteria a requirement for organic nutrients as sources of energy, *i.e.*, they are *heterotrophic*. Lacking chlorophyll (a photodynamic pigment which enables the *autotrophic* green plants to utilize solar energy in the manufacture of carbohydrates from water and carbon dioxide), fungi are dependent upon enzyme systems to derive energy from organic substrates. They therefore are either *saprobes* or *parasites*. Their complex and multiple enzyme systems enable them to play essential roles as scavengers in the destruction of cellulose, various carbohydrates, and nitrogenous substances which accumulate on the earth's surface with the death of autotrophic plants and heterotrophic animals and insects. Their preeminent ability to break down complex organic substrates of almost every type is an important and essential activity in the recycling of carbon and other elements in the cycle of life.

We accept the opinion of many taxonomists that the fungi were derived from ancestral forms among the *Protista* (see Chapter 2) rather than from primitive plants. We therefore refer to those fungi which grow on dead organic substrates as *saprobes* rather than saprophytes, a term which implies plant relationships.

These destructive activities are undesirable when molds cause "tropical deterioration" of fabrics, leather, electrical insulation and other manufactured goods, and extensive losses may follow failure to protect material from the ravages of fungi in warm humid climates.

Mold (fungal) and bacterial spoilage of food is a more familiar problem to the marketer of agricultural produce and to the housewife. To reduce or prevent such spoilage, some fruits and vegetables must be marketed and used within a short interval after maturation; millions of dollars are spent in refrigerating trucks, freight cars and storage plants; food products are pasteurized or sterilized and packed in hermetically sealed cans before they are offered to the consumer; and preservatives (*e.g.*, calcium propionate in bread) are added to foods to prolong their marketable palatable condition. Most of these fungi which cause deterioration of fabrics or spoilage of food are not known to invade tissues of man.

Saprobic Habitats of Pathogenic Fungi. The natural habitats of most of the fungi which cause systemic mycoses are in organic wastes or debris, or in soil enriched by organic wastes. In suitable (and usually restricted) habitats, these fungi grow and compete successfully and persistently with other microorganisms of the soil. The pathogenic fungi are true

saprobes, but under appropriate conditions, as when inhaled or introduced subcutaneously by puncture wounds, they can become at once pathogenic in either a normal person or a patient debilitated by disease. The subject of saprobic habitats of pathogenic fungi has been mentioned in the Introduction, and it is discussed at length in Chapter 4 and at appropriate places in later chapters.

INDUSTRIAL USES OF FUNGI

Food. Throughout the world edible wild or domesticated varieties of mushrooms (Basidiomycetes) are important additions to the menu. Truffles, the fleshy fruiting structures of one group of the Ascomycetes, also are highly prized delicacies. Duggar (1905) reported that in 1901 Munich was the principal mushroom market of Europe, that 31 species were sold in its markets, and that the total crop for that year was nearly 1,000 tons. The extent of the industry and the occasional inclusion of toxic species led to regulation of sales and reduction in the number of permitted species. Many people collect and eat many species of wild mushrooms today, but the commercial market in the United States is limited to one variety of *Agaricus* (*Psalliota*) *campestris*. Commercial production of this mushroom in the United States during the year ending June 30, 1968 totaled 181,000,000 lbs. (USDA Rept. Service, Vg 2–1–2, 8/68), at a value to growers of $61,750,000. Fungi are elements in the natural food supplies of some wild animals. Yeast is a food supplement which fortifies the diet with vitamins and other nutritional elements. Besides these direct supplements, such molds as species of *Penicillium* complete the ripening of certain varieties of cheese and are responsible for the characteristic flavors of Roquefort, Camembert, Gorgonzola and Stilton cheeses, for example.

The use of fungi to alter the texture, improve the flavor, and increase the palatability and digestibility of natural or processed foods has been exploited much more widely in the Orient than in the United States. Hesseltine (1965, 1967) and visiting scientists from Japan, Malaysia and Indonesia have studied these processes in the laboratory in the United States. Shoyu (soy sauce) is prepared from wheat and soybeans. Hydrolysis of soybean protein by *Aspergillus oryzae* is followed by a *Lactobacillus* fermentation, followed by a yeast fermentation, and by ageing. Substitution of chemical hydrolysis of the soybean shortens the duration of the process. But as carried out in Japan, where shoyu has been manufactured for more than 1,000 years, the entire process may require two years. Tempeh, prepared by growth of *Rhizopus oligosporus* on soybeans, and Ontjom, prepared by growth of *Neurospora sitophila* on peanut press cake, are important foods in Indonesia. Many other Oriental foods depend upon enzymatic hydrolysis of starch and protein by fungi and upon fungal fermentations.

Fermentations. From the most remote times man has used as beverages the juices of fruits fermented by wild yeasts. In industrialized societies, fermenting strains of yeasts are selected for productivity and flavor. Selected strains of *Saccharomyces cerevisiae* and other species are used for brewing and baking. In baking, alcoholic fermentation causes bread dough to "rise," producing the desired porous texture of the loaf.

Besides potable and edible products of fermentation, yeasts yield industrial alcohol (*Saccharomyces*), fats (*Endomyces*) and proteins (*Torulopsis utilis*).

A mold (*Fusarium*) can produce within 48 hours, 12 to 15 grams of fat from a liter of a 50 per cent glucose solution. Molds are used also in the production of citric, oxalic and gluconic acids (*Aspergillus niger*) and itaconic acid (*A. itaconicus*). These or other acids are produced under suitable conditions by many other molds.

Antibiotics. Since Fleming's observations and investigations of microbial antagonisms in contaminated culture plates, culminating many years later in the commercial production of penicillin, this aspect of the metabolic activities of fungi has been vigorously exploited. TC Publication 248 of the U. S. Tariff Commission "Synthetic Organic Chemicals, United States Production and Sales, 1966" states that in 1966, 9,652,000 pounds of antibiotics were produced for human and all other uses, and that sales in these markets totaled $99,263,000 for the same period. The costs of research and development expended during the past 20 years by private industry, in government subsidized research, in government laboratories, in the search for fungi yielding antibiotics, and in making these antibiotics suitable and available for clinical use, must be estimated in the billions of dollars.

PLANT PATHOLOGY

Unlike the diseases of man and animals, most of the plant diseases generally seen by the gardener are caused by fungi, although there are also important viral and bacterial diseases of plants. Fungal diseases of plants include "damping-off" which destroys seedlings, many blights, leafspots, mildews, galls (excluding those caused by insects), rusts, and systemic diseases such as the smuts. Fungi damage timber in the forest and lumber after it has been processed. They destroy fruits, vegetables and cereal grains before and after marketing. Their versatility and adaptability are demonstrated by the appearance of more virulent or more resistant strains of fungi which replace those previously controlled by methods developed by the phytopathologist and geneticist. The enormous losses in the potential world food supply, and the research and technological costs of controlling fungus diseases in the field and protecting harvested crops and processed foods from spoilage, cannot be estimated with accuracy.

SCIENTIFIC VALUES OF MYCOLOGY

A full appreciation of the importance of fungi must include recognition of their didactic values. In order to propagate fungi in the laboratory, the mycologist and the biochemist have selected, devised and utilized hundreds of varieties of natural and synthetic culture media. These include such natural substances as carrot and potato plugs; such artificial substrates as decoctions and derivatives of plant and animal tissues, peptone-carbohydrate mixtures and many chemically defined culture media designed for precisely controlled experimental studies. Most of the fungi can be maintained in the laboratory on one or many of these media. The almost infinite variety and complexity of forms and metabolic activities of the fungi have given the biologist insight into problems of growth, morphology, reproduction, antibiosis, genetic inheritance, nutritional requirements and metabolic pathways in a segment of life more amenable to observation and experi-

mental manipulation than the higher plants and animals. The fungi provide excellent demonstration and experimental materials for high school, college, post-graduate research and industrial laboratories. They are adaptable and effective tools in the hands of the biochemist and they provide him with accurate and sensitive bioassay methods.

MEDICAL IMPORTANCE

Antibiotics. The advent of antibiotics has had an enormous impact upon medical mycology. The therapeutic effectiveness of antibiotics has focused attention upon actinomycetes and fungi which produce them. The potentialities of fungi for production of new, less toxic, more specific or more effective antibiotics has stimulated extensive surveys of fungi collected from all parts of the world and representing all the major systematic groups in a search for more productive varieties of species already used in commercial production and for other species which may yield new antibiotics.

The brilliant record of antibiotics in decreasing the severity of illness and preventing fatalities in many infectious bacterial diseases has stimulated the hope for eventual chemotherapeutic control of the mycoses. This goal has, in fact, been partially achieved since the discoveries of nystatin, amphotericin B and saramycetin (also known by code numbers X-5079C and RO2-7758). The clinical use of these antibiotics in oral, gastrointestinal and systemic mycoses and the remarkable effectiveness of griseofulvin in the treatment of dermatophytoses will be reviewed at appropriate places in following chapters.

Ergot. Just as utilization of beverages and foods modified or produced by fungi extends into the prehistoric past, so some of the drugs of present pharmacologic importance have had their origins in ancient medicine and folklore. Ergot is an example of a fungal product with profound toxic characteristics which, at proper dosage levels, has long held an important place in pharmacopoeias. Ergot is the resistant, over-wintering stage of *Claviceps purpurea*, a fungal pathogen of rye, which transforms the seed of that plant into a compact spur-like mass of fungal pseudo-tissue (the sclerotium). This is the ergot of commerce. Ergot contains five or more optically isomeric pairs of alkaloids. The levorotatory isomers are active in inducing uterine contractions, controlling bleeding and alleviating certain localized vascular disorders, *e.g.*, migraine headaches.

Toxins. There is no natural division of the fungi into edible "mushrooms" and toxic "toadstools," nor are there any simple tests such as the difficult separation of the upper layer of the mushroom cap and the ability to tarnish silver which reliably characterize the toxic mushrooms. The most generally recognized toxic genus, *Amanita*, includes some edible species and, conversely, a few mushrooms which are eaten with impunity by most persons who collect and eat wild mushrooms (mycophagists), produce gastrointestinal disturbances in some persons. Many wild mushrooms and other types of fleshy fungi surpass in delicacy of flavor the mushroom of commerce. If one wishes to eat these mushrooms, however, it is essential that he accurately identify each species, that he sample each newly tested species separately and in small quantity at first, and that he select for the table only young fresh specimens.

Several species of the mushroom genera *Psilocybe* and *Amanita* have been

highly prized and utilized in religious and social rites by some primitive societies because they induce intoxication and hallucination. The pharmocologic and therapeutic properties of these fungi have been studied and both crude and purified derivatives have been given clinical trials and merit further study. See Chapter 4 for a further discussion of the toxins of fungi.

Mycoses of Man and Animals. Finally, the most immediate concern of the medical mycologist is with those fungi which cause disease and death in man. As previously indicated there are 15 to 20 important mycoses of man (plus as many more of less severity or frequency) caused by more than 100 species of fungi. These diseases vary from the superficial skin infections such as dermatophytosis and cutaneous candidiasis to generalized mycoses such as coccidioidomycosis and histoplasmosis.

The tables of Vital Statistics of the United States show that within the reporting areas of the United States the total number of deaths reported as due to scarlet fever, typhoid, whooping cough, diphtheria, dysentery and malaria fell from 10,165 in 1941 to 267 in 1966. During this twenty-five-year period the number of deaths reported as due to mycoses rose from 324 to 393. Deaths in the United States for all causes in 1941 were 1,397,642, and for 1966 were 1,863,140.

The decrease in deaths from some of the bacterial and parasitic diseases can be attributed to their control by vaccination, improved sanitation or chemotherapy. At the same time, the reported deaths from mycoses have maintained an approximately constant numerical ratio to the general increases in population and deaths. Several factors influence the interpretation of these data. Since 1956 many cases of mycotic disease have been treated successfully with amphotericin B. During this period, however, increased awareness of mycoses on the part of clinicians and pathologists, wider availability and use of laboratory diagnostic procedures, and improved stains in the pathology laboratory have probably increased the number of diagnosed fatal mycoses. At the same time there probably has been a real increase in the number of mycoses in persons whose susceptibility to fungal infections has been increased by administration of immunosuppressive drugs and by treatment of nonmycotic diseases with corticosteroids or broad spectrum antibiotics. Further, the aged patient, whose life span has been extended by treatment of cancer or other debilitating disease, is more susceptible to secondary fungal infection than a young, vigorous individual. Two additional opposing factors decrease the accuracy of data on fatal mycoses. The rapid growth of a fungus such as *Candida albicans* in a debilitated patient with a nonmycotic disease may be a minor factor as a cause of death, yet be so apparent in the terminal course of the disease that it is reported as the actual cause of death. On the other hand, lack of experience in the laboratory, and inadequate laboratory study and autopsy examination, may prevent the recognition and reporting of many mycotic deaths.

The clinical diagnosis of a mycosis must usually remain provisional pending observation and identification of the fungus in smears, tissue sections or culture. Demonstration of a rise and fall in specific antibodies provides presumptive evidence. Lacking these laboratory studies, the diagnostic study must exclude such chronic bacterial diseases as tuberculosis, many febrile illnesses, Hodgkin's disease, sarcoidosis, leukemia and malignancies. The differential diagnoses for various mycoses will be discussed in later chapters.

Aside from their better recognition, the most important medical problem associated with the mycoses is their therapy. Until recently most of the systemic mycoses could be offered only supportive therapy. Today griseofulvin has shortened and improved the therapy of superficial but resistant mycoses such as tinea capitis and onychomycosis. Sulfonamides, 2-hydroxystilbamidine, amphotericin B and saramycetin have greatly improved the prognosis in the generalized mycoses, but antimycotics which are less toxic and more effective must still be sought before the therapeutic problems in the mycoses are solved.

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Chapter 2

Characterization of the Fungi and Actinomycetes

CLASSIFICATION AND MORPHOLOGY

Phylogeny. Naturalists of the 17th century, one hundred years before Linnaeus, speculated about the systematic position of fungi among living organisms. Darwin's announcement in 1858 of a plausible theory of evolutionary development among existent and antecedent forms of life, stimulated many phyletic studies of fungi. From what ancestral forms did fungi arise, and can the divergent morphologic specialization of fungi be explained in a rational phylogenetic schema?

Traditionally the fungi have been classified as primitive plants, and the subdivision, Thallophyta, of the plant kingdom included the autotrophic algae and the heterotrophic fungi. Morphologic similarities between reproductive structures suggested that some groups of fungi might have been derived at one or more points from the green algae, and that others were derived from marine red algae, by loss of chlorophyll and assumption of heterotrophic nutrition. These morphologic similarities may well be the result of parallel evolution only, but loss of chlorophyll does occur in green algae. It is recognized, *e.g.*, that Prototheca is derived from Chlorella by such a loss. Recent reports of cutaneous and systemic infections in man and animals caused by Prototheca have intrigued medical mycologists, although it is recognized that Prototheca is an achloric alga and not a fungus.

There is a strong and increasing tendency among taxonomists to exclude the fungi from the plant kingdom. Recognition of only two kingdoms appeared to early naturalists concerned principally with higher plants and animals, to be rational. This concept continued to dominate systematic classification long after the study of primitive forms of life revealed the difficulties of assigning such microorganisms as protozoa to either the plant or animal kingdoms. As early as 1860 Hogg proposed a third kingdom, *Regnum Primigenum*, and proposed the term, *Protoctista*, to designate these primitive forms. Haeckl, in 1878, placed the fungi in the *Protistenreich*. Among modern mycologists, Martin (1955) challenged the still widely held concept that fungi were primitive plants, and he gave a comprehensive historical review of this aspect of fungal taxonomy. Copeland (1956) proposed four kingdoms, and he placed in *Kingdom Protoctista* the algae (except blue-green algae), protozoa, slime molds and fungi.

Whittaker (1969) has modified and extended the system of Copeland by creating a fifth kingdom for the fungi. His five kingdoms are: *Monera* (bacteria, actinomycetes and blue-green algae), *Protista* (10 phyla which