MEDICAL MYCOLOGY

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Preface

THE medical and public health importance of diseases caused by fungi and an apparent increase in their frequency have stimulated an intense interest in mycoses. Case reports, improvements in diagnostic methods and significant physiologic and taxonomic studies are recorded in journals scattered through the literature of a dozen specialties. Rapid advances in knowledge of the epidemiology, clinical aspects and therapy of mycoses and the increasing importance of mycoses in the differential diagnosis and care of chronic granulomatous diseases have made Medical Mycology a dynamic specialty.

There are now available several excellent mycologic monographs, texts and chapters of textbooks, but we believe there remains a need for a textbook to emphasize the epidemiologic aspects of the subject and to adequately bridge the chasm between the complex discipline of Mycology and its medical applications. If we have been able to present a fresh approach to Medical Mycology to emphasize its essential unity with general Mycology and to review and clarify some of the epidemiologic relationships which characterize it and make medical mycology such a fascinating subject of research and practice, we have achieved our immediate goals.

Dr. Binford wrote Chapter 5 and the sections on pathology in chapters on specific mycoses. Dr. Utz wrote portions of the sections on clinical aspects and therapy of mycoses in Chapters 16, 20 and 21 and critically reviewed other corresponding sections. The senior author must assume responsibility for most of the content and style of the book. We are particularly indebted to Dr. D. J. Winslow for writing the section on pathology in the chapter on Mycetomas and for critically reviewing the drafts on pathology in the other chapters. Dr. Arden Howell critically reviewed early drafts of Chapters 8 and 9 and made useful suggestions which were included in the final drafts. We are indebted also to our colleagues, Drs. John E. Bennett, George W. Lones, Herbert F. Hasenclever and Roger D. Goos who read the entire typescript, pointed out errors or omissions and contributed valuable corrections. Many other colleagues have encouraged and helped the authors in the preparation of the book.

Mrs. C. W. Emmons patiently typed numerous revisions of all chapters. We are indebted also to Miss Katherine Steele who, working under the restrictions imposed by Federal employment (as did the authors), devoted evenings and week-ends to typing the final revision and proofreading it.

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the dermatophytoses were supplied by Dr. P. H. Jacobs, as indicated for each such illustration. Nearly all of the photographs illustrating histopathology were taken by Dr. Binford in the course of routine studies of mycotic cases which had been sent to the AFIP for consultation. Our thanks are expressed to that Institute for the use of this material and to its Photographic Division for the technical work. Special thanks are given to Dr. Harry I. Lurie, South African Institute of Medical Research, Johannesburg, Africa, for his contribution of some of the histopathological material used in illustrating sporotrichosis, and to Dr. J. P. Wiersema, Pathologist, Government Hospital, Paramaribo, Surinam, for case material on Lobo's disease. Some of the illustrations, as indicated, have been published previously, and we are grateful for permission for their reuse here.

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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 *Sporotrichum 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 chromoblastomycosis was reported as an important but rare disease and the clinical importance and high fatality rates of South American blastomycosis 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 taxonomic errors.

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 saprophytes 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 numbers of fungi physiologically adapted to either localized or systemic parasitism of plants far exceeds the numbers 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 200,000. Among these fungi there are at least 18 valid species which cause systemic and potentially fatal mycoses, 12 which cause severe localized subcutaneous or lymphatic infections and about 20 which cause superficial infections of the skin, its associated keratinized tissues or the mucosa, and which penetrate only rarely to deeper tissues. Fungi which capture amebae and nematodes 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 50 or more species of fungi which are generally recognized as pathogens of man, it is firmly established that under unusual circumstances 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, increased susceptibility in a patient under treatment with steroids 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 for man can be expressed at the present time only in general terms of tolerance to temperatures of 35 to 37° C. and the possession of enzyme systems which adapt them to parasitism of animal hosts.

With few exceptions the grave, systemic and subcutaneous mycoses are caused by fungi which are essentially free-living saprophytes in nature. These mycoses are not contagious, and infection in man and animals follows inhalation or traumatic implantation of the fungi from their normal saprophytic 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 saprophytes, and only by accident pathogens of man, is the rule rather than the exception in medical mycology. Recognition of the saprophytic nature of the 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 rodents, between *Histoplasma* and excreta of chickens, 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.

Chapter

1

Role of Fungi in the Economy of Nature

The Fungi

Definitions.—Fungi are heterotrophic microorganisms of simple structure without anatomical organization into roots, stems or leaves. They are differentiated from the autotrophic algae by lack of chlorophyll, a photodynamic pigment which enables the algae to manufacture food from water, CO_2 and minerals in the presence of sunlight. Since fungi are heterotrophic, they are obligate saprophytes or parasites with nutritional requirements similar to those of bacteria.

Fungi differ from the bacteria in their greater size and more complex morphologic development. This differentiation may consist of oval cells which reproduce by budding, or of long tubular, septate hyphae which exhibit apical growth and true lateral branching. Reproduction may be purely vegetative or it may be associated with the production of elaborate morphologically specialized structures which facilitate fertilization and the protection or dissemination of the resulting spores or zygotes. The spore-bearing structures may be simple lateral branches of the hypae or they may be organized into such elaborate large reproductive bodies as the mushrooms and bracket fungi which protect the spores as they develop and facilitate their dispersal at maturity.

It is easy to point out similarities between certain of the bacteria (e.g., the diphtheroids and mycobacteria) and such microorganisms as *Actinomyces Nocardia* and *Streptomyces*. These three genera are frequently classified as higher bacteria, but they resemble fungi in apical growth and branching, they include species which cause diseases with clinical and histologic similarities to the mycoses, they are commonly studied by the mycologist and they include species which cause some of the human diseases which will be discussed in later chapters of this book.

There are other points at which specialized bacterial groups approach certain primitive or reduced fungi in morphology, suggesting possible relationships, and one might postulate phylogenetic lines from bacteria based upon development of increasing specialization and complexity. However, some fungi resemble autotrophic green algae and others suggest evolutionary origins from marine algae. Another viewpoint excludes the fungi from the plant kingdom and postulates their origin from protozoal ancestry. The theory which probably is most generally accepted postulates the systematic position of the fungi upon a polyphyletic evolutionary development, with origins at more than one place among the protozoa and the autotrophic algae. We shall not go further into this interesting but speculative question of the evolutionary origins of the fungi.