Second Edition

Medical Mycology

The Pathogenic Fungi and The Pathogenic Actinomycetes

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Photograph facing the title page: A "jungle" of *Candida albicans* on cornmeal Tween agar.

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Note to the Reader

A set of three color filmstrips on *Medical Mycology* is available from the publisher. The filmstrips are for individual use and teaching purposes, and nicely complement this textbook.

The three filmstrips (A, B, and C) consist of a total of 220 separate frames. For your convenience, the slide numbers and their corresponding text figure numbers are listed here.

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Preface to the Second Edition

"Tempus fugit." This adage of life also applies to medical mycology. Since the publication of the first edition there have been many and significant changes in many areas of fungal disease. This has necessitated significant revision in almost all sections of this book and complete rewriting in many areas. As reflected in the Chapter Six "introduction to the science of mycology," our understanding of taxonomy has been greatly altered by research on methods of conidiation in the fungi. Our understanding of the basis for the varied manifestations of clinical disease has also changed. This is nowhere more apparent than in perhaps the most famous mycotic infection, histoplasmosis. The interaction of this parasite of low virulence with the cellular defenses of the individual host with all its nuances causes vastly different disease to occur from one patient to another. An attempt has been made to categorize and synthesize this new information into useful clinical classification schemes. In the area of antimycotic therapy, some significant additions to our roster of useful drugs are now appearing. The imidazoles have promise of greatly altering our ability to counteract fungal invasion. The new drug ketoconazole is being found useful in chronic *Candida* infections, paracoccidioidomycosis, and perhaps in the entire spectrum of the mycoses. Its great advantage is that it can be given orally. Some of the established imidazoles such as miconazole are found efficacious in *Pseudallescheria* and other infections that had no useful treatment previously. Also, flucytosine is now being noted as the drug of choice in chromoblastomycosis and other infections by dematiaceous fungi. It is expected that other, more tolerable antimycotic agents for systemic disease will be forthcoming. These topics, in addition to new insights into basic mechanisms of fungal pathogenicity, have made this an exciting decade in medical mycology. An overview of all these advances and conceptual changes is included in the present text.

I would like to thank the many people who have assisted me in preparing this second edition. Particular gratitude goes to Daila Shefner, who has thoroughly gone over this manuscript, translated my spelling into that used in the English language, and kept an eye on the grammar and syntax. Great thanks go to J. W. "Bill" Carmichal and Mike McGinnis for keeping my taxonomy reasonably straight and to my mentor in medical mycology, L. Ajello, for his many suggestions, corrections, cultures, photographs and pieces of information. Although we do not always agree, our conversations are always lively and provocative. I am very grateful to Janet Gallup for the pictures of the laboratory contaminants used in Part Five of the book and to all others whose photographs appear herein. The sources of all photographs are acknowledged where known. However in the interchange of teaching material among

colleagues the original source of an illustration is sometimes lost. For this I apologize.

Basically the same format has been used in this current edition as in the first. References are concentrated in the late 1970's for current information unless previous ones are of historical interest, establish a significant point, or remain the best review of a particular topic.

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Preface

The purpose of this volume is threefold: (1) to provide a basic presentation of the subject matter of medical mycology; (2) to present an overview of research efforts concerning both the fungal pathogen and its host; and (3) to serve as a reference source for both historical and current literature of importance in the development of the field. In this way it is hoped that this text will be found useful to students at all levels—the professional medical mycologist, the investigator in this and related disciplines, and the clinician and pathologist who may be concerned with fungous diseases only occasionally or whose practice involves frequent encounters with the mycoses. There is presently a renewed interest in mycotic diseases, particularly in the so-called opportunistic infections, and in basic research on host-parasite interactions. For this reason, it was felt that a text should be designed to include these recent developments in the field of medical mycology and to provide a fundamental understanding of the diseases and the organisms that cause them. It is hoped that this text will provide such an expanded view of the subject.

The history and development of medical mycology are characterized by several stages. In the days of Gruby, Malmsten, and Schoenlein, around 1840, there was a wave of excitement in this new field, and investigators were determining the fungal etiology of several dermatologic diseases, such as the tineas and thrush. A few years later, the sister field of bacteriology began to overshadow clinical mycology because of the trail-blazing work of Koch and Pasteur, and the study of fungal disease went into its first decline. The critical investigator was replaced by the dilettante, and in that period many papers appeared describing dozens of new fungal pathogens (generally contaminants) and attributing a fungal etiology to everything from warts and acne to psoriasis and pemphigus.

In the early 1900's, this dermatologic and mycologic chaos was brought into order temporarily by a dermatologist who was also a scientist. Sabouraud's monumental work on the tineas cleared the air, and he set forth the principles of medical mycology: careful observation of the disease, critical evaluation of its etiology, and a cautious, unbiased approach to therapy. Soon after this, however, there was another period of decline and confusion. There were by then some 130 synonyms for *Candida albicans* and descriptions of more than 300 dermatophyte species in 40 genera. Beginning in the late 1930's, however, trained mycologists, such as Conant and Emmons, began working in the field and placed the nomenclature of the etiologic agent and evaluation of the disease syndrome on a scientific basis. Conant's lucid *Manual of Clinical Mycology* became the bible of the discipline and was later joined by the works of Emmons

and Lacaz. These works clearly defined and described the pathogenic fungi as well as the diseases they produce and remain standard texts in the field.

Beginning in the early 1960's, a new aspect of medical mycology has emerged and gained increasing importance. This is the growing incidence of opportunistic fungous infections. To a large extent, this has paralleled advances in medicine involving the treatment of neoplasms, collagen diseases, and other debilitations as well as the progress made in organ transplantation. Such techniques prolong the life of the patient but abrogate normal host defenses and frequently allow saprophytic species to proliferate and invade, thereby causing disease.

In this volume I have generally approached the subject matter along traditional lines used in previous textbooks of medical mycology. In addition, I have tried to emphasize the growing importance of opportunistic infections and to delineate the differences between pathogenic and opportunistic infecting fungi and the diseases they elicit.

Another area of great importance in medical mycology is the increased basic research aimed at elucidating the physiology, biochemistry, and mechanisms of pathogenicity of the fungi in addition to the responses of the host when challenged by infection. An overview of some of this work is included in the appropriate chapters. This is not intended to be a review of all investigations in a particular field but only an indication of some areas in which active research is being carried out. Sections are also included concerning both natural and experimental infections in animals. I have tried to compare and contrast the diseases as they occur in man and animals, and in this way I hope that the text will be useful in the study of both human and veterinary mycology. In addition, there are chapters on other important aspects of medical mycology, such as the pharmacology of antimycotic agents, allergic diseases, intoxications, the genetics of pathogenic fungi, and taxonomy.

In choosing the references to be included in the various chapters, I have elected to pick those that illustrate two aspects of the subject. The first group includes the historically significant papers that first described a disease or some important facet of it. It has been very rewarding and sometimes amusing to read original literature on a particular disease. Papers up to 1960 that are still pertinent or whose content has not been updated by more recent investigations or reviews have been included. The second criterion for choice of a paper was its recentness and significance in the field. Most of the references cited have appeared since 1960. These papers not only include new information but also review previous publications and thus act as a bibliography for those interested in a particular subject.

I am profoundly and deeply grateful for the assistance of Dr. Josephine Morello. She has patiently transformed (translated) the language of my manuscript into readable English. This has been done after many hours of writing, rewriting, and debating, leading to deletion and compromise. The reader should be aware that if he finds this text at all readable it is because of her arduous efforts.

I also wish to thank my board of consultants, Libero Ajello, E. S. McDonough, Angela Restrepo, Shirley McMillen, and Howard Larsh, mycologists; Sharon Thomsen, Francis Straus, and Philip Graff, pathologists; Francisco Battistini and Allan L. Lorincz, dermatologists; John Fennessy, radiologist; and Nicholas J. Gross and Frederick C. Kittle, specialists in diseases of the chest. I would also like to thank Martha Berliner, P. Kulkavni, C. Satyanarayana, F. Mariet, S. Banerjee, and F. Pifano, among others, for the use of illustrations.

Special thanks go to my friend and associate in many research projects, Edward D. Garber, who has contributed the chapter on genetics and taxonomy.

The maps were prepared by Robert Williams and the drawings by Robert Williams, Charles Wellek, and John Rippon. A final thank you is given to Daila Shefner for proofreading this manuscript.

JOHN WILLARD RIPPON

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Introduction to Medical Mycology

The ability of fungi to cause disease appears to be an accidental phenomenon. With the exception of a few dermatophytes, pathogenicity among the molds is not necessary for the maintenance of dissemination of the species. Further, the fungi that are able to cause disease seem to do so because of some peculiar trait of their metabolism not shared by taxonomically similar species. Thus the survival and growth of fungi at the elevated temperature of the body, the reduced oxidation-reduction environment of tissue, and the ability to overcome the host's defense mechanisms set apart these few species from the great numbers of saprophytic and plant pathogenic fungi.

Among the best examples of this transient adaptation to invasion and growth within tissue are the dimorphic fungi. In nature they grow as soil saprophytes, usually in a restricted ecologic niche, producing mycelium and conidia similar to other fungi. However, when their conidia are inhaled or gain entrance by other means into man or other animals, the organisms are able to adapt and grow in this unnatural environment. In so doing, drastic changes occur in their morphology, metabolism, cell wall content and structure, enzyme systems, and methods of reproduction. If the host's defenses are unable to counteract the organism — and this is rare — the infection leads to the death of both host and parasite. Infection for the fungus is a blind alley and is not contagious to other hosts or generally of use in disseminating the species. Such diseases include histoplasmosis, blastomycosis, coccidioidomycosis, and, to a degree, sporotrichosis. The previously mentioned also represent primary pathogens among the fungi in that they are able to cause disease in a normal healthy host, provided that sufficient numbers are present in the infecting dose. In debilitated hosts, their course of infection and disease is exaggerated.

The second major group of fungus diseases are the dermatophytoses. This is a closely related group of organisms with the ability to utilize keratin and to establish a kind of equilibrium, albeit transitory, with the host. In the soil are numerous related keratolytic species, most of which seldom, if ever, are recovered from clinical disease. Others, especially the anthropophilic species, are universal agents of ringworm and probably no longer have a significant soil reservoir, depending on human or fomite contact for transmission. These are among the commonest infectious agents of man. The dermatophytes are in a sense specialized saprophytes, as they do not invade living tissue, utilizing only the dead cornified appendages of the host, such as hair, skin, nails, fur, and feathers. Dermatophytosis may be considered a colonization of cornified structure by such organisms. The clinical disease caused by the dermatophytes is, for the most part, a toxic and allergic reaction by the host to the presence of the organisms and its by-products.

A group of diseases referred to as the subcutaneous mycoses include chromoblastomycosis, mycetoma, sporotrichosis, and entomophthoromycosis. These are organisms of limited invasive ability, gaining entrance to the body by traumatic implantation, and may take years to produce a noticeable disease, requiring that much time to adapt to the tissue environment. The clinical course is a chronic progressive one and very slow to develop. Mycetoma or madura foot and chromoblastomycosis are clinical entities

that may have a number of different species as etiologic agents. Mycetoma in particular may be caused by a diverse group of bacterial and fungal organisms that are totally unrelated to one another, but the clinical disease elicited is similar. The organisms are all soil saprophytes of regional epidemiology.

There remains a large category of opportunistic fungous infections. Included are diseases that are manifest almost exclusively in patients debilitated by some other cause and whose normal defense mechanisms are impaired. Formerly, some of these diseases and the fungal infections were in almost constant association such as mucormycosis with diabetes, candidiasis with hypoparathyroidism and other endocrine disturbances, and aspergillosis with chronic lung disease. In present-day medicine, the advent of cytotoxic drugs, long-term steroid treatment, and immunosuppressive agents has markedly increased the number and severity of diseases in this category. The diverse array of organisms being isolated from these cases emphasizes that probably all fungi may be considered potential pathogens when normal defenses are sufficiently abrogated. Fungi are particularly remarkable for their ability to adapt and propagate in a wide variety of environmental situations; thus their invasion of debilitated patients is not surprising.

Also included in this book will be a brief discussion of conditions arising from ingestion or inhalation of fungal products. These include allergic manifestations to conidia, such as farmer's lung and coniosporosis; toxic reactions due to consumption of infected food products, such as aflatoxin; and, of universal interest, mushrooms and mushroom poisoning.

HISTORY

Medical mycology is a science with traditions as any other specialty of human endeavor. For this reason, some bacterial diseases are included in this text. For many years actinomycetes were considered a "link" between bacteria and fungi. The diseases they produce were chronic granulomatous diseases similar to true mycotic infections. Morphologically, physiologically, and biochemically the actinomycetes are bacteria. Further, they are sensitive to antibacterial antibiotics to which fungi are insensitive, but not to antifungal drugs. Because of similarities in clinical disease, however, the pathogenic actinomycetes are treated along with eumycotic infections.

The discovery of the causal relation of certain fungi to infectious disease precedes by several years the pioneer work of Pasteur and Koch with pathogenic bacteria. Schoenlein and Gruby studied the fungus of the scalp infection favus *(Trichophyton schoenleinii)* in 1839, and in the same year Lagenbeck described the yeastlike organism of thrush *(Candida albicans)*. Robert Remak had described favus earlier, but his work was ignored. Gruby even isolated the fungus of favus and produced the disease by inoculating a healthy subject, thus fulfilling Koch's postulates before Koch formulated them. Prior to this, Bassi described the fungal etiology of muscardine of silkworms (*Beauveria bassiana*).

In spite of its earlier beginnings, medical mycology was soon overshowed by bacteriology and has never received as much attention, though some of the fungous diseases (dermatophytoses) are among the more common infections of man. This is perhaps attributable to the relatively benign nature of the common mycoses, the rarity of the more serious ones, and the difficulty of differentiation of these structurally complex forms which, in a practical sense, sets them off sharply from the bacteria.

A great impetus was given the study of fungous diseases by the careful work of perhaps the most famous name in the field of medical mycology — Raymond Sabouraud. The publication of the classic work on dermatophyte infections, "Les Teignes," was a model of scientific observation. Unfortunately, his followers were not as careful, and the literature became cluttered with numerous synonyms for almost every fungus infection and with a fungal etiology for almost every human disease. There are over 100 names given for the yeastlike organism, *Candida albicans*. Some true fungous infections (histoplasmosis and coccidioidomycosis) were at first described as caused by protozoan parasites, but the works of Ophuls, Brumpt, Gilchrist, and Smith (most of them dermatologists) delineated their true nature and the extent of their epidemiology. A group of Latin American scientist-clinicians is responsible for a large portion of our present knowledge. This group includes González Ochoa, F. Almeida, Mackinnon, and others. The terrible confusion in nomenclature was finally brought into order by the work of the outstanding mycologists, Norman Conant and Chester Emmons. Present research is aimed

toward improved diagnostic techniques, specific serologic tests for fungous diseases, accurate taxonomy, and new and improved chemotherapeutic agents. Moreover, efforts are being made to elucidate the mechanisms of fungal pathogenicity. The field of medical mycology is indeed fortunate, now, to have a number of competent investigators directing their attention to the problems of this discipline.

PATHOGENIC FUNGI

Today we recognize some 175 "pathogens" among the approximately 100,000 species of fungi — about 20 that may cause systemic infections, about 20 which are regularly isolated from cutaneous infections, and a dozen that are associated with severe, localized, subcutaneous disease. In addition, there is a long list of opportunistic organisms that may cause disease in the debilitated patient. A few of the diseases discussed in this book, e.g., actinomycosis, candidiasis, and pityriasis versicolor, are caused by endogenous organisms, i.e., species that are part of the normal flora of man; all other fungous and actinomycetous infections are exogenous in origin.

The criterion of pathogenicity is one of the poorest that can be used in differentiation of microorganisms. Because pathogenicity is variable and difficult to determine, by its use parasitic microorganisms are grouped together that are, in fact, much more closely related to certain free-living forms than they are to one another. The superficial nature of pathogenicity as a differential characteristic is nowhere better illustrated than among the fungi. The pathogenic forms which constitute the subject matter of medical mycology form a heterogeneous group that includes some of the actinomycetes, certain molds and moldlike fungi, and a number of yeasts and yeastlike organisms. As stated before, very few are primary pathogens, i.e., able to produce disease in a healthy host, and infection is a blind alley for the organism. With the possible exception of perhaps a half dozen anthropophilic dermatophytes, none of this group is an obligate parasite, and most are misplaced soil saprophytes. From a general biological point of view, then, the pathogenicity of certain fungi is of very minor significance; from the point of view of the parasitized host, man, it is of considerably greater interest. Thus, for lack of a better definition, a fungal pathogen will denote an organism regularly isolated from a given disease process; rarely, isolated organisms from a variety of clinical circumstances will be considered opportunistic organisms (Table 1).

Mechanisms of Pathogenesis

The mechanisms of fungal pathogenesis have been the subject of considerable basic research. The two major physiologic barriers to fungal growth within tissue are temperature and redox potential. Most fungi are mesophilic and have an optimal growth range considerably below the temperature of the human body. Similarly, the majority of fungi are saprobic and their enzymatic pathways function more efficiently at the oxidation-reduction potential of nonliving substrates than at the relatively more reduced state of living metabolizing tissue. In addition, the body has a highly efficient set of cellular defenses to combat fungal proliferation. Thus, the mammalian species have remained rather free of obligate parasitism by the fungi throughout evolutionary history. Even the so-called "true pathogenic fungi" that are able to grow and proliferate at the temperature and redox potential of the human body are of relatively low virulence. Thousands of cases of infection or infestation by *Histoplasma* or *Coccidioides* occur each year, but only a few result in a frank disease process. It must be concluded that spontaneous resolution is the norm in such infections and that any disease elicited by any fungus is an "opportunistic infection"; some defense of the host was insufficient when challenged. For the fungi of even lesser virulence (*Cryptococcus, Aspergillus, Mucor,* and so forth), the defect in the host's defense must be even greater. These organisms, though thermotolerant, are less metabolically efficient in living tissue and thus require greater advantage (a greater host defect) in order to adjust to this environment and proliferate. Fungal species and strains that are not thermotolerant, cannot adjust to the tissue environment and cannot withstand even a debilitated host's defenses are thus unable to invade and cause disease. Conversely, the basic mechanism of fungal pathogenicity is its ability to adapt to the tissue environment and temperature and withstand the lytic activity of the host's cellular defenses.

A wide spectrum of adaptability exists among the various agents of the human mycoses. Within the group termed the "true

Table 1 *Clinical Types of Fungous Infections**

Type	*Disease*	*Causative Organism*
Superficial infections	Pityriasis versicolor	*Malassezia furfur*
	Piedra	*Trichosporon beigelii* (white)
		Piedraia hortae (black)
Cutaneous infections	Ringworm of scalp, glabrous skin, nails	Dermatophytes (*Microsporum* sp., *Trichophyton* sp., *Epidermophyton* sp.)
	Candidiasis of skin, mucous membranes, and nails	*Candida albicans* and related species
Subcutaneous infections	Chromoblastomycosis	*Fonsecaea pedrosoi* and related forms
	Mycotic mycetoma	*Pseudallescheria boydii*, *Madurella mycetomatis*, etc.
	Entomorphthoromycosis	*Basidiobolus ranarum*
		Conidiobolus coronatus
	Rhinosporidiosis	*Rhinosporidium seeberi*
	Lobomycosis	*Loboa loboi*
	Sporotrichosis	*Sporothrix schenckii*
Systemic infections	Pathogenic fungous infections	
	Histoplasmosis	*Histoplasma capsulatum*
	Blastomycosis	*Blastomyces dermatitidis*
	Paracoccidioidomycosis	*Paracoccidioides brasiliensis*
	Coccidioidomycosis	*Coccidioides immitis*
	Opportunistic fungous infections	
	Histoplasmosis	*Cryptococcus neoformans*
	Aspergillosis	*Aspergillus fumigatus*, etc.
	Mucormycosis	*Mucor* sp., *Absidia* sp., *Rhizopus* sp., *Rhizomucor* sp.
	Candidiasis (systemic)	*Candida albicans*
	Pseudallescheriasis	*Pseudallescheria boydii*
Miscellaneous and rare mycoses and algosis	Phaeohyphomycosis	*Wangiella dermatitidis*, *Phialophora* sp., etc.
	Hyphomycosis	
	Algosis	*Paecilomyces* sp., *Beauveria* sp., *Scopulariopsis* sp. etc.
	Basidiomycosis	*Prototheca* sp.
		Schizophyllum commune, *Coprinus* sp., etc.

pathogenic" fungi, the ability to adapt to a tissue environment is quite marked and is expressed as thermal dimorphism. The organisms grow as mycelial fungi producing conidia at room temperature, but at 37°C they are transformed to a completely different morphologic state, a so-called parasitic phase. In three of the true pathogenic fungi, budding, yeastlike cells are formed (*Histoplasma, Blastomyces,* and *Paracoccidioides*); in the fourth *(Coccidioides),* an endosporulating spherule is formed. In the parasitic state the metabolic rate of the organism increases several fold and different sets of metabolic pathways are favored. This results in a rapidly growing, rapidly multiplying organism whose cell wall structure, carbohydrate content, lipid composition, and RNA aggregates are completely different from those of the organism growing at lower temperatures. These new entities are quite susceptible to phagocytosis and killing by mammalian macrophages, however. Therefore most infections are aborted and resolve spontaneously. Blastomycosis may be an exception to this.

As already noted, the other group of systemic infecting agents, the "opportunists," require a greater defect in the normal defenses to become established. They do not demonstrate thermal dimorphism; they are temperature tolerate, however, and strains isolated from human infection are metabolically more active at 37°C and in the redox potential of human tissue than are isolants of the same species from soil.

A gamut of adaptability is also seen among the agents of the subcutaneous mycoses. These agents are of low virulence capacity and require mechanical introduction of the organism into tissue (traumatic implantation) before they can manifest a disease process. In *Sporothrix schenckii,* the most virulent of the low virulent organisms, transformation to a yeastlike stage accompanies this adaptation to tissue growth, another case of thermal dimorphism. With the agents of chromoblastomycosis and mycetoma, much time is required for this adaptation, and a different morphological form is finally produced. This is the planate-dividing "sclerotic cell" in chromo-