Fungi Pathogenic for Humans and Animals

(IN THREE PARTS)

PART B

Pathogenicity and Detection: I

EDITED BY

Dexter H. Howard

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Introduction to the Series

Mycology is the study of fungi, that vast assemblage of microorganisms which includes such things as molds, yeasts, and mushrooms. All of us in one way or another are influenced by fungi. Think of it for a moment—the good life without penicillin or a fine wine. Consider further the importance of fungi in the decomposition of wastes and the potential hazards of fungi as pathogens to plants and to humans. Yes, fungi are ubiquitous and important.

Mycologists study fungi either in nature or in the laboratory and at different experimental levels ranging from descriptive to molecular and from basic to applied. Since there are so many fungi and so many ways to study them, mycologists often find it difficult to communicate their results even to other mycologists, much less to other scientists or to society in general.

This Series establishes a niche for publication of works dealing with all aspects of mycology. It is not intended to set the fungi apart, but rather to emphasize the study of fungi and of fungal processes as they relate to mankind and to science in general. Such a series of books is long overdue. It is broadly conceived as to scope, and should include textbooks and manuals as well as original and scholarly research works and monographs.

The scope of the Series will be defined by, and hopefully will help define, progress in mycology.

Paul A. Lemke

Foreword

The occurrence of mycosis as primary or secondary disease is rising rapidly. This is due, on the one hand, to increased clinical awareness and improved diagnostic skills and, on the other, to increased use of antineoplastic and immunosuppressive drugs. The diagnostic and therapeutic problems posed by mycoses strongly influence medicine today. To combat these problems, a better understanding of the ability of fungi to invade susceptible hosts, the immunological and serological changes evoked by fungi, and currently available antifungal drugs is essential. This book, the second of three parts, meets that need exactly. It contains the latest and most authoritative information on pathogenic mechanisms, immunology, serology, antifungal drugs, and fungal toxins.

The authors are prominent figures in their fields with outstanding research records. Professor Howard is a leading mycologist who has made important contributions to our knowledge of host-parasite interactions. He is also a noted teacher who has trained many young scientists in the field.

Microbiologists and clinicians alike will find this book most useful and appreciate its thorough coverage of theory and practice in the mycoses.

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Preface

The attribute of the zoopathogenic fungi that makes them especially interesting—their ability to evoke pathological changes in a susceptible host—will be the subject of the second volume of this series. Because there are so many topics of interest under such a heading, a third part is being planned.

The overall format of Part B has chapters on theoretical treatments of a subject followed by a consideration of practical consequences. For example, the chapter on Humoral Responses of the Host is followed by one on Serodiagnosis, and the chapter on Mode of Action of Antifungal Drugs is accompanied by one on Measurement of the Activity of Antifungal Drugs.

For the most part, I have tried to be internally consistent in matters of nomenclature. Thus, the terminology set forth in Part A has been adopted for Part B. There may be some disagreement with the choices. I have adopted the recommendations set forth in Memorandum No. 23 of the Medical Research Council, London. [Medical Research Council. 1977. *Nomenclature of Fungi Pathogenic to Man and Animals*, Memorandum No. 23 (4th ed.), Her Majesty's Stationery Office, London, 26 pp.] In certain especially controversial areas I have indicated synonymous alternatives. I trust each individual author's splendid coverage will overshadow any undetected nomenclatural oversights by the editor.

Again, as in Part A of this series, I gratefully acknowledge the indispensable assistance of Mrs. Lois F. Howard. Her insistence on the accuracy of textural detail was again unfaltering. I am grateful to her, to Ms. Judy Fung, and Ms. Bette Y. Tang for the numerous typings and retypings a work of this sort requires. Some support for this venture has been supplied by research grant AI 16252 from the National Institutes of Allergy and Infectious Diseases, National Institutes of Health, which is used to fund the Collaborative California Universities-Mycology Research Unit (CCU-MRU).

I am most grateful to the splendid group of authors who collaborated with me to produce this volume.

Dexter H. Howard

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Contents of Part A

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Pathogenic Mechanisms of Mycotic Agents

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I. INTRODUCTION

During the past 140 years, which encompass the modern history of medical mycology, considerable information has been acquired about human mycoses. In this time period all the major diseases were described and, especially to the casual observer, substantial knowledge of these diseases in the areas of etiology, epidemiology, and diagnosis was gathered. During the past three to four decades major progress has been made in understanding these diseases in such areas as immunology, pathology, predisposing factors, serology, and therapy. With this reservoir of available information, medical personnel often gain the impression that the once poorly understood mycoses can now be discussed at length by any competent medical mycologist. However, when confronted with the seemingly simple question, "How do these organisms cause disease?", the medical mycologist agrees that little is known and that much more must be learned of disease processes to help potential or existing patients.

Before writing this chapter we decided that it should not be a depressing thesis on how little is known in the area of fungal pathogenesis but, instead, it should be from the point of view that this is an area that is just beginning to be investigated. It is an area that *must* be examined in greater depth and, indeed, an area to which many investigators have already made substantial contributions.

In some regards medical mycologists are in a better position than most people cur-

rently perceive. We are fortunate to have colleagues who, in related fields such as medical microbiology and plant pathology, have investigated problems and gathered considerable information for decades on the pathogenesis of diseases caused by other microbes [259, 358-360]. Of course, not all of the accumulated concepts are directly applicable to our field, but many methods, approaches, and hypotheses can be used to assist the medical mycologist in elucidating similar problems today.

One purpose of this chapter is to present a comprehensive list of references of classical and recent contributions in the field of pathogenesis. By so doing we hope that it will encourage others to delve further into this field. New ideas, approaches, and models, and more concerted efforts are needed in this area; perhaps some of our thoughts will act as incentives to future workers in this field.

To understand pathogenicity one must first place it in the proper framework of symbiosis. *Symbiosis* is a Greek word which means living together: *sym* means together and *bios* means life. There are three generally accepted manifestations of symbiotic relationships. One is *commensalism*, in which one organism benefits but neither is dependent metabolically upon the other. A second form of symbiotic relations is *mutualism*, where both organisms are dependent metabolically upon one another. The third form of symbiosis is *parasitism*. A parasite is an organism that is dependent metabolically upon a host and contributes nothing to the host; in fact, destruction of cells usually results. A parasite may be nonpathogenic or pathogenic. The symbiotic relationships mentioned are diagrammed in Fig. 1.

Pathogenicity is the capacity of an organism to damage, i.e., to produce disease in another animal or plant. This process is considered to be the result of direct interaction between the pathogen and host. Although there are some microbes that produce materials which can alter or potentially destroy cells in another organism, it is not considered that such organisms are pathogens unless they directly interact with a host. For example, some bacteria (e.g., *Clostridium botulinum*) and some fungi (e.g., *Aspergillus* spp.) produce toxins independently of a host, and thus are not genuine pathogens. However, should it eventually be demonstrated that *Aspergillus* spp., for example, in fact produces myotoxins in vivo, then such organisms would have to be reclassified as genuine pathogens. Such distinctions are worthy of note in order to realize that a disease process cannot be fully understood if one studies only a host or only a given pathogen, i.e., as separate entities. In fact, a disease process is the culmination of an interaction between at least two organisms and the resulting interaction may be totally different from the independent

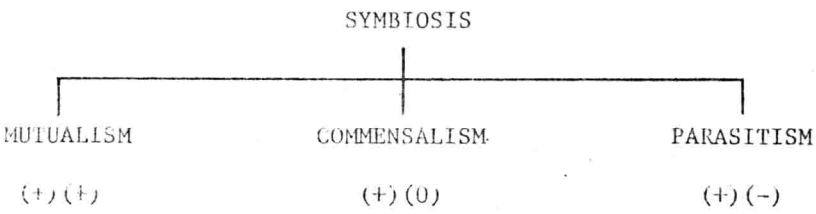

Figure 1 Potential modes of symbiosis: (+), organism benefits from the relationship; (-), organism is harmed by the relationship; (0), organism neither benefits nor is harmed by the relationship.

actions of either of the organisms. This is why, for example, it is not enough to demonstrate that a pathogenic fungus can produce materials in vitro which can harm, alter, or destroy cells in a potential host. If such a material is produced while the organism is actively metabolizing *in* another organism (i.e., in vivo), then there may be a disease process. Additionally, it is not sufficient to demonstrate that a host can respond to an organism unless such a response can be shown to be either destructive or protective.

For an organism to cause disease it must (1) enter the host, (2) multiply in host tissues, (3) resist or not stimulate host defense mechanisms, and (4) damage the host. Products of organisms which produce factors that assist in the accomplishment of one or several of these processes are called *virulence factors.* Since a pathogen must accomplish all four of these processes, and each process is complex, several determinates (virulence factors) are usually necessary to create the overall effect, i.e., to initiate a disease process. It is these properties of animal mycotic agents that will be examined in this chapter; responses to these and other factors on the part of the host are covered as separate entities in this book under sections dealing with immunology and pathology. Thus, this chapter is limited to properties of fungi that are known, or speculated to be, virulence factors in the disease process in animals. The limitation of this chapter to these factors is for practical purposes and must not be considered as a restriction of the overall goal, namely, to elucidate mechanisms and interactions that result in the final process: disease.

This chapter is divided into two areas. The first, consisting of Secs. II to XIV, covers all of the major and some of the minor human mycoses with reference to published reports on factors produced by pathogenic fungi which may play a role in the virulence of the etiologic agent. In many areas reports on virulence factors of the pathogens do not exist. By revealing the paucity of information on a given organism, we hope that investigators will accept this as a challenge to investigate such areas. In the second portion of this chapter, Sec. XV, we make brief mention of numerous factors that are not *classically* considered to be virulence factors. However, in our opinion, they do represent properties that potentially pathogenic fungi must possess in order to function in a disease process. Also, included are a few views of our colleagues in related fields, with the hope that perhaps some of these ideas will stimulate the reader to investigate pathogenesis in the human mycoses.

II. MYCETOMA, ACTINOMYCOSIS, AND NOCARDIOSIS

A. Description and General Pathogenesis

Mycetoma is a clinical syndrome characterized by a chronic, granulomatous pseudotumor, involving the cutaneous and subcutaneous tissues as well as bone. In advanced cases, the affected body area becomes deformed and multiple, draining sinuses or fistulae develop in the tumor. Pustular exudate containing pigmented granules or colonies of the infecting agent(s) is discharged from the tracts. The triad of tumefaction, draining sinuses, and grains or granules is used to define the disease mycetoma [314].

There are at least six actinomycetes and 16 species of true fungi that are capable of causing mycetoma [103]. The disease is considered to be actinomycotic or eumycotic depending on the nomenclature of the etiologic agents demonstrated. Agents of mycetoma have been isolated from soils everywhere, but North Africa, the Mediterranean region, and Mexico appear to be the main endemic areas.

The disease is believed to be acquired by traumatic implantation of the infectious

agent into skin or subcutaneous tissues. The time required for the development of mycetomas is variable and is dependent on the infecting agent and host response. Initial symptoms may appear several months to years after actual inoculation, and the mycetoma may continue to develop slowly for as long as 25 years [252].

Cases of mycetoma have been reported worldwide [1,103,252,314]. Eumycotic mycetomas reported from the temperate areas of the world are most commonly caused by *Petriellidium boydii,* formerly named *Allescheria boydii* [251]. The imperfect or conidial phase of this fungus is known as *Monosporium (Scedosporium) apiospermum* [103]. Strains of this fungus as well as some species of the higher bacteria that cause actinomycotic mycetoma display a wide range of virulence and have been isolated from a variety of clinical syndromes [238,252,257,318,395].

Actinomycosis is a chronic, suppurative, or granulomatous disease involving the cervicofacial, thoracic, or abdominal areas. The disease is characterized by the development of firm, board-like lesions that develop draining sinus tracts. Characteristic "sulfur" granules or grains are discharged from the drainage tracts. The cervicofacial form of the disease may be described as a mycetoma of the jaw [44]. The higher bacteria *Actinomyces israelii* and *A. bovis* are the accepted etiologic agents. The disease is found worldwide due to the endogenous nature of the infecting agents, which are found as normal oral flora. Factors that convert an infection into a disease state are unknown.

Nocardiosis is an acute or chronic, suppurative disease characterized by primary pulmonary involvement with possible hematogenous dissemination to various organs. It has a predilection for the central nervous system and may manifest itself as an encephalitis or meningitis. The accepted etiologic agent is the soil actinomycete *Nocardia asteroides,* although *N. brasiliensis* [314] and *N. farcinica* [103] also have been reported in a few cases. Recently, Mahajan et al. [248] reported a reproducible, reliable method of producing pulmonary nocardiosis in monkeys by inoculating the animals via the lower canaliculus. Consistent morbidity, lung pathology, and mortality were reported, and the authors proposed using this model for further studies in the pathogenesis of this disease.

Although nocardiosis is generally recognized as a primary pulmonary infection produced following inhalation of the organism, some species of *Nocardia* cause actinomycotic mycetomas. In 1973, Gonzalez-Ochoa [142] studied the virulence of three species of *Nocardia* by inoculating them into the feet of mice. He reported that the mouse footpad route yielded chronic, progressive, fistulous tumors that affected bone and produced granules. The lesions did not heal spontaneously as did the nodules produced by other inoculation routes: intraperitoneal, intramuscular, intravenous, intradermal, or subcutaneous. This work was later substantiated by testing additional strains in a similar manner [143]. Stretton and Bulman [380] also have reported the experimental induction of mycetoma. Using rabbits, these workers were able to induce granule-producing tumors, typical of human mycetoma, by subcutaneous or intramuscular inoculations of a variety of actinomycetes.

Attempts to produce experimental eumycotic mycetomas have been frustrating. Murray et al. [273] claimed success in inducing murine mycetoma and granules with *Madurella mycetomatis,* but Cavanagh [57] was unable to reproduce the results. Repeated intracutaneous and subcutaneous inoculation of a monkey's palmar aspect resulted in only a transient lesion, with no granule formation and eventual spontaneous healing [57]. Recently, however, Mahgoub [249] reported the successful development of mycetoma tumors with *M. mycetomatis* in athymic nude mice. Grains appeared as early as 9 days

after footpad inoculation, were well developed by 21 days and were similar to human grains in pigment and tissue reaction. The author also noted that immunologically competent mice were resistant to infection by actimomycotic or eumycotic agents, and that infection could be produced only in athymic mice.

B. Pathogenic Mechanisms

A number of pathogenic factors in this array of organisms have been delineated. The mycetoma agents do not form randomly wandering hyphal filaments in vivo; they form thick-walled grains or granules. The mycetoma grain is not a disorganized collection of hyphal filaments but has a consistent specific shape, composition, and color [83]. It is composed of an agglomeration of actinomycotic filaments or fungal hyphae of differing density. Many mycetoma grains are characteristic of specific etiologic agents [44]. The ability of mycetoma-inducing organisms to grow as grains in vivo is related to the fact that both host and parasite take part in their development; thus, the presently unknown host-parasite interaction produces conditions conducive to development of granules rather than the growth of free actinomycotic filaments or eumycotic hyphae by these pathogenic organisms [252].

In 1963, Zamora et al. [428] reported the isolation of two immunologically active polysaccharides from *Nocardia asteroides* and *N. brasiliensis.* The first somatic polysaccharides isolated from each species were chemically similar and thus were defined as group-specific; however, the second group of polysaccharides (composed of arabinose, galactose, and mannose, but in different molar ratios) reacted only with homologous serum. The polysaccharides were species-specific and aided the diagnosis of the organism as well as the stimulation of host responses.

Numerous "aggressins," such as spreading factors, toxins, and enzymes, have been implicated in the pathogenicity of bacterial diseases. While testing numerous fungi for the presence of collagenase, an enzyme capable of degrading collagen and therefore a potentially key virulence factor, Rippon and Lorincz [319] found that *Actinomadura madurae,* an agent of actinomycotic mycetoma, produced this enzyme in vitro. This was the first report of collagenolytic activity derived from a pathogenic actinomycete. In a later study Rippon and Peck [320] using mutant strains of *A. madurae,* demonstrated in vivo a direct relationship between the amount of collagenase production and the virulence of the organism. A year later Rippon and Varadi [321] reported the first isolation of the enzyme elastase from cultures of several dermatophytes, but were not able to detect any elastase activity in tested mycetoma-causing actinomycetes. Staat and Schachtele [368] reported the detection of dextranase-producing strains of *Actinomyces* in human dental plaque. This enzyme may influence the synthesis and metabolism of carries-related dextrans.

Another potential virulence factor of some mycetoma-inducing agents is a capsule. Mackinnon et al. [247] have reported the production of a capsule around very young cultured cells of seven strains of *Phialophora (Exophiala) spinifera* and *P. (E.) jeanselmei.* The capsule showed a variable thickness and could not be removed by washing the cells in water. The chemical composition and structure of this capsule as well as its role in the pathogenesis of mycetoma are yet to be discovered.

Another area investigated recently has been the immunologic activity and specificity of a water-soluble extract from *N. opaca.* Adam et al. [2] reported the isolation of a soluble immunoadjuvant extracted from the cell walls of *N. opaca* following lysozyme treatment of lipid-free cells. The main biological activity of this material was reported

to stimulate an increase in the amount of circulating antibodies to ovalbumin in guinea pigs. Further studies of this extract by Bona et al. [39] revealed that it acted on bone marrow-dependent lymphocytes and was a nonspecific activator of B-lymphocytes, similar to the lipopolysaccharide of gram-negative bacteria. Further analysis revealed that stimulation of B-lymphocytes by this extract produced IgM synthesis and polyclonal proliferation that was not dependent on previous exposure to or infection by the organism.

III. DERMATOPHYTOSES

A. Description and General Pathogenesis

Dermatophytoses, superficial infections caused by dermatophytes, are characterized by itching, flaking, and sometimes inflamed patches of skin, loss of hair, or nail invasion. The etiologic agenst are members of a closely related group of fungi which are classified into three genera: *Microsporum, Epidermophyton,* and *Trichophyton* [305]. As a group, dermatophytes are found worldwide, even though many species are limited geographically [3,4,293,399]. Although the diseases caused by dermatophytes are not fatal, they comprise one of the most common infections of humankind. One recent study revealed that 73.5% of almost 4000 mycoses diagnosed and analyzed in a 1-year period in India were dermatophytoses [194].

The dermatophytes can be divided into three main groups depending on their natural habitats: anthropophilic, when humans are the natural host; zoophilic, when a variety of animals act as natural hosts; and geophilic, when soil is the natural habitat [23]. Dermatophytic zoonoses (transmission of infection from animal reservoirs to humans) have been reported [106,148,199,288,355,406] and are of increasing concern to those involved with public health and dermatophyte containment and control.

Dermatophytes usually invade and parasitize only the nonliving, keratinized layers of skin, nails, and hair. This highly developed host-parasite relationship is responsible for a multitude of clinical manifestations. For example, the prominent feature of dermatophytic infections of the skin, apart from broken hairs and dystrophic nails, is the varying degrees of inflammatory and eczematous reactions which these infectious agents provoke in the host [23,148]. Many of these host-parasite interactions are dependent on specific moieties and enzymes produced by many dermatophytes, a subject discussed in greater detail later in this section.

As mentioned earlier, the dermatophytes are classified into three genera. Each of the genera is characterized by having specific "target tissues" which it infects. Species of *Microsporum* infect hair and skin, *Epidermophyton floccosum* infects skin and nails, and species of *Trichophyton* attack hair, skin, and nails [44]. The reasons for this observed tissue specificity are unknown, but may prove to be related to specific nutritional requirements or enzyme production by individual organisms. Although reliable animal models for the study of dermatophytoses are few [72,200,343], studies of dermatophyte pathogenesis using models may answer some of these pressing questions.

B. Pathogenic Mechanisms

One of the more thoroughly investigated areas of fungal pathogenesis has been the dermatophytoses. Beginning around 1962, two groups of investigators started definitive studies on the structures of antigens from dermatophytes and attempted to establish a relation-

ship between fungus structure and immunological activity. Barker and his associates initially studied glycopeptides, discovering that immediate hypersensitivity reactions were induced by the carbohydrate moiety and delayed hypersensitivity was elicited by the protein moiety [22,27]. Recently this group also has examined the structure of an isolated galactomannan-peptide allergen [22]. Bishop, Blank, and their associates have studied both polysaccharides and proteolytic enzymes from dermatophytes [149], and most recently, Nozawa's group has examined the immunochemical characteristics of purified polysaccharide-peptide complexes [285]. This area of research is reviewed by Grappel et al. [148] and Gander [132].

Lipid moieties of microorganisms have been known to cause some occasional host responses. Numerous phospholipids have been isolated from *Trichophyton rubrum* [77], and some investigations of the sensitizing properties of dermatophytic lipids have appeared in the literature. Andersson et al. [8] have reported that lipid fractions of trichophytin, a cell wall extract of dermatophytes, elicited positive allergic delayed skin reaction in sensitized guinea pigs. The free fatty acid fraction proved the most allergenic but was significantly less reactive than the polysaccharide-peptide fraction. The middle-chain fatty acids (C_{10}-C_{12}) showed the greatest allergenic activity among the fatty acid group [166]. The authors suggested that fatty acids may act as contact sensitizers and may be responsible for the skin reactivity induced by some dermatophytoses.

Self-synthesized enzymes may serve fungi in many ways. They may enhance survival in tissues by chemically or physically altering the immediate environment, or they may act directly by digesting host proteins, thus providing a source of nutrition. Rippon and Varadi [321] reported that one strain of *Microsporum gypseum* and several species of *Trichophyton* produced the enzyme elastase which permitted these fungi to utilize elastin, a component of human tissue. An additional survey by Rippon [312] revealed several more species of dermatophytes that had elastase activity. One strain of *Trichophyton schoenleinii* produced enzymes capable of solubilizing the three scleroproteins: keratin, elastin, and collagen [319]. In general, the elastase enzyme was produced by organisms isolated from clinical cases which were characterized by marked inflammation. This concept was later substantiated and enlarged upon with some modification by Hopsu-Havu and co-workers [172,173]. They noted the production of urease and sulfatase in strains of *E. floccosum*. Interestingly, pleomorphic cultures were more active enzyme producers than were granular forms.

Recent investigations by Yu et al. [426,427] have revealed the production of three keratinases (I, II, III) by *T. mentagrophytes* var. *granulosum*. Keratinase I has been shown to digest unautoclaved white guinea pig hair by removing the medulla of the hair and producing cortical fissures. Keratinases II and III are cell bound and are immunologically dissimilar from keratinase I and each other. The pathogenic role of the two cell-bound enzymes is unknown at present.

Kunert [214,215] studied the proteolytic activity and products of keratin degradation by a strain of *M. gypseum*. He noted three phases of degradation: the initial phase, characterized by rapid growth, digestion, and increase in proteolytic activity; the middle phase, characterized by a decrease in the rate of phase one activities; the final phase, defined by a new increase in substrate decomposition but with a continuing decrease in other parameters examined [214]. The principal products of the keratinolysis were simple peptides. Further study by Kunert [214] on *M. gypseum* and by Ruffin et al. [330] on *Keratinomyces ajelloi* revealed the production of additional enzymes by dermatophytes. Sulfite

is capable of splitting disulfide bonds of keratin and of producing S-sulfocysteine and possibly cysteic acid [330]. Kunert [215] proposed that keratin may be denatured and made digestible to exoproteases by such "sulfitolysis." Ruffin et al. [330] further proposed that proteolytic digestion and sulfitolysis may occur simultaneously. The issue is still under investigation.

In 1972, Nobre and Viegas [283] reported that over 75% of freshly isolated strains of *M. gypseum, M. canis, E. floccosum,* and *T. mentagrophytes* were lipase producers. Although the authors failed to relate lipase production and activity to pathogenesis, Das and Banerjee [78] reported that a strain of *T. rubrum* secreted lipase and phospholipase A when grown in Sabouraud's broth. They noted that phospholipases may play an important role in maintaining the function of the cell membrane and may aid dermatophytic invasion of host cells.

In addition to purely enzymatic studies of dermatophytes, the pattern of host invasion by these fungi has been observed microscopically. English [104,105] has described the in vitro invasion of keratin by dermatophytes. Using a light microscope, she noted that the invading mycelia were flattened, branched fronds that forced themselves beneath cuticular scales. A more recent electron microscopic study by Baxter and Mann [31] revealed that eroding dermatophytic hyphae first digested the poorly resistant endocuticular region of hair. The exocuticle layer was eroded next, leaving the resistant epicuticle. The observations indicated a concerted enzymic and physical attack on host tissues. Most recently, a report by Farley et al [110] examined the origin and ultrastructure of intrahyphae of *T. terrestre* and *T. rubrum.* Further research is required in this area, but present data at least suggest that the emergence of intrahyphal hyphae during dermatophytic infection may favor fungal survival in vivo in spite of a host-protective immune response, and thus act as an additional virulence factor in many dermatophytic infections.

IV. ASPERGILLOSIS

A. Description and General Pathogenesis

Aspergillosis may exist in many diverse disease forms. The true spectrum of syndromes has been described by Conant et al. [63] who state: "Aspergillosis . . . is characterized by the presence of inflammatory, granulomatous lesions in the skin, external ear, nasal sinuses, orbit, eye, bronchi or lung, and occasionally in the nasopharynx, vagina, uterus, heart valve, pleural cavity, mediastinum, bones, brain, and meninges." All forms of aspergillosis are found worldwide in humans. The etiologic agents are members of the ubiquitous, large genus *Aspergillus.* The vast majority of these organisms are soil and air saprophytes. The most common etiologic agents of human infections are *Aspergillus fumigatus* and *A. niger,* although *A. flavus, A. oryzae, A. glaucus,* and *A. nidulans* also have been implicated, as well as numerous other species.

Aspergillosis actually represents a group of diseases that has been divided into three categories: (1) allergic, (2) colonizing, and (3) invasive. Rippon [314] has further separated the diversity of forms into the following syndromes: pulmonary, disseminated, central nervous system, cutaneous, nasal orbital, and iatrogenic. Numerous reports in the literature support this classification as well as the premise that aspergillosis, in general, is an opportunistic infection primarily affecting debilitated, immunologically altered patients [20,50,94,258,270,310,328,402]. Allergic aspergillosis is a syndrome that has acquired more attention recently [167], but we will not discuss it in this chapter.