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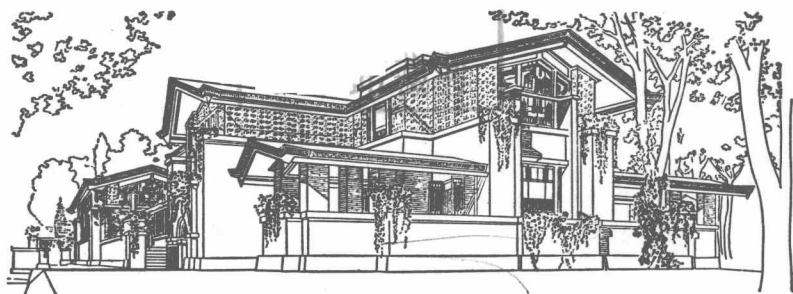
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DISSEMINATING FUNGUS DISEASES OF THE LUNG



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FOREWORD

When the author of this book completed a two year internship at the Cook County Hospital, Chicago in 1910 the organisms responsible for the diseases he now presents, except histoplasmosis, had been discovered. However, the number of reported clinical cases was relatively small. In fact, in the 1912 eighth edition of Osler's *Principles and Practice of Medicine* is the following statement: "Much attention has been paid lately to the local and general infections caused by the group of fungoid organisms variously classed as Streptothrix, Actinomyces, Cladothrix and leptothrix. The French workers, who have done so much lately, group the various diseases caused by these organisms under the term Mycoses, which is a convenient and useful designation. Four or five of these diseases are of sufficient importance to be considered in a work of this scope." Those discussed were actinomycosis, sporotrichosis, nocardiosis, oidiomycosis, mycetoma and aspergillosis.

Inasmuch as the mycoses produce lesions which more closely resemble those of tuberculosis than the other nontuberculous infections, many persons with fungus diseases were labeled tuberculous and sent to sanatoriums as was also true of those with some other conditions including sarcoidosis. The only two findings to justify the diagnosis of tuberculosis, namely the recovery of tubercle bacilli and the reaction to tuberculin, often were not employed. Failure to use these diagnostic procedures was especially lamented by Krause in 1928 in an article entitled, "Remarks on the Laboratory Diagnosis of Pulmonary Tuberculosis." Even among those who did use them, over-emphasis was placed on the physical findings and x-ray shadows of pulmonary lesions. Indeed, in persons who had such physical signs or x-ray shadow findings, inability to recover tubercle bacilli or to elicit the tuberculin reaction often was used to condemn these truly diagnostic procedures.

As late as 1956, 7.2 per cent of the patients in a sanatorium for the tuberculous were found to have "serologically proved" histoplasmosis and in 33 per cent of these cases, *Histoplasma capsulatum* was demonstrated. On the basis of the findings in this one institution it was estimated that there were probably 1200 persons in institutions for the tuberculous in the histoplasmosis area.

Thus when Dr. Greer entered the practice of medicine and accepted a medical school teaching position, little was known about such items as prevalences, geographic distribution and treatment of fungus diseases. In fact, at that time diagnosis of a pulmonary fungus disease usually justified grave prognosis.

Early in his practice and teaching career Dr. Greer became especially interested in the mycoses. He employed all differential diagnostic procedures as they were established and over the years assembled many accurately diagnosed cases. In addition, he kept abreast of medical literature and thus became highly qualified not only in diagnosis but also in all other aspects of fungus diseases. This continued rich experience with and study of mycoses for more than 50 years has been brought together in such a concise and laconic manner as to give the reader brief histories of each disease, geographic distribution, epidemiology, pathogenesis, clinical manifestations, diagnosis, prognosis and treatment with a minimum amount of reading time. Numerous well chosen illustrations and appropriate reference lists enhance the value of the book. It is a privilege to recommend this thoroughly authentic book for reading and study of physicians everywhere.

J. A. MYERS, M.D

PREFACE

While great progress has been made in the clarification and simplification of mycological literature, the classification of fungi has not reached a comparably satisfactory stage. Interpretation of many mycological phenomena of immunity is uncertain, which is surprising since mycology had an earlier beginning than bacteriology and virology, and, in the latter, more fundamental contributions have been made than in mycology. Despite the fact that one of the polysaccharides responsible for the development of immunologic changes was isolated from fungi (*Trichophyton* and *blastomyces*), the mechanisms of immunity are not simplified to the same degree as they have been in many such bacterial infections as tetanus, diphtheria, and botulism.

More knowledge is needed of the basic fundamental components of systemic fungi. The therapeutic agents, including amphotericin B, are fungistatic. Fungicidal effects follow indirectly and slowly, from metabolic attrition, or by the inclusion of adjuvants. There is little doubt of the value of amphotericin B as a fungistatic drug in inhibition of the growth of yeast and yeast-like fungi, but, as has been previously stated, the agent does not possess direct fungicidal activity. Newer antibiotics are needed or drugs with better penetrating and fungicidal power.

There are many problems for research mycologists and clinicians, and it would consume a great deal of time to mention all of them, even if the author were conversant with them all. The intent, instead, is to discuss a few of the difficulties known to the clinician and the mycologist. These are: (1) the reason the capsule of *Cryptococcus neoformans* loses its pathogenicity in cultures and whether its pathogenicity resides within the capsule; (2) exact data in regard to natural immunity; (3) why the acquisition of agglutinins does not confer resistance to the pathogenic effects of *Candida albicans*, and why, although agglutinins, precipitins, and complement-fixing antibodies have been found in pa-

tients with cryptococcal infections, it remains unproved whether they confer any resistance to the infection; (4) the reasons for the fluctuations in virulence of *Candida albicans* from strain to strain about which nothing is known; (5) why, when skin hypersensitivity in fungus infections to whole yeast, and to extracts of the fungus, can often be demonstrated, the exact significance and occurrence are inconstant, and, sometimes, there are inexplicable differences in the reactivity of the whole yeast phase and the histoplasmin antigens in the complement fixation test in histoplasmosis; (6) whether there is an agent in nonsterile soil which interferes with obtaining *Blastomyces dermatitidis* in cultures, whereas the fungus can be isolated in sterile soil. It is problematic whether competitive microorganisms (actinomycetes) could be operative against *Blastomyces dermatitidis* in nonsterile soil, and render the fungus dormant or inactive until activated by favorable climatic conditions; (7) why certain fungus diseases are confined within rather narrow geographic areas; (8) the fundamental reasons for cross reactions, as for instance in North American blastomycosis, histoplasmosis, coccidioidomycosis, and other heterologous fungi, and whether antigenic similarity is the reason.

It is plausible that biologic and therapeutic problems are intimately related, and the efficacy of therapy of fungus diseases depends upon a consideration of both factors. Although empirical and surgical methods of treatment will perhaps always be used, and quite properly, the mainstay for the control and treatment of these diseases must be sought in better understanding of the fundamental basic problems involved in each patient and in every type of mycotic disease. The discovery of amphotericin B denotes progress, but, as stated before, although of fungistatic benefit for yeast and yeastlike fungi, especially cryptococcal meningitis and histoplasmosis, it is not a panacea for all mycotic diseases.

The author is of the opinion that the clinician has a prominent function in the effort to control and, perhaps, to cure the severe types of fungus diseases. His observations of the early manifestations, the varying clinical patterns, the course, and the comparative value of diagnostic tests and procedures are vital. Because of his training and experience, it is he who is expected to suggest the diagnosis, initially, and furthermore, from his co-operation

with the clinical pathologist and mycologist, the diagnosis may be established. The author believes in the main, that the clinician is in the first line of defense, and his contributions are valuable. Dodge, in the *Annals of the New York Academy of Sciences* (1950) stated, "By 1935, the principal fungi associated with human disease had been described. Since that time, we have been largely filling in details rather neglecting the morphology and cytology of the organism, and turning our attention to pathology and therapeutics and to the nutrition of fungi. . . . We need better clinical description and classification, correlated with a careful study of the organism isolated in each case before we can assume the same clinical entity is produced by several different fungi. . . . We should recognize the possibility in fungus infections of a symbiosis of two or more organisms, perhaps complicated by endocrine dysfunction, especially of the thyroid."

It is not the author's intention to convey the impression that many of the present and future problems are unsolvable. Differences of opinion are helpful and constructive, and may lead to the acquisition of more knowledge, while an attitude of mental serenity and acquiescence will stultify progress. Such differences of opinion among mycologists as those relative to taxonomy, the pathogenicity of systemic mycoses, and the invasiveness of some fungi, and the absence of invasion in others, are but a few of the dissident views which will someday be solved.

The passage of time will, perhaps, bring to fruition the combined efforts of forward-looking scientific and observant men and women who delve into the intricacies of the known and unknown of mycotic diseases. Many rewarding discoveries will surely be made in the years to come; however, a truly Utopian viewpoint would be required for belief that the millennium of scientific knowledge will be reached in the current life span or for many generations to follow. The main objective is one of initial control of these diseases, and, when this goal is reached, the same mastery of the ravages of disease may be achieved as has been accomplished in many bacterial diseases.

ALVIS E. GREER, M.D.

INTRODUCTORY REMARKS

Thirty-five years ago, the author became aware of the importance of fungus diseases of the lungs when he read Doctor Mary Lapham's article in 1926 on the subject of the association of such diseases with pulmonary tuberculosis. At that time, and for many years later, he was Chief of Staff of a large County Tuberculosis Sanatorium, and, through that experience saw the beginnings of clinical awareness of their significance in the diagnosis of disease of the chest, which awareness was to progress steadily throughout the subsequent years.

During a period of six years, 1930-1936, on careful investigation 18 cases of proved systemic mycoses were found among 306 patients consecutively admitted to the sanatorium. Judging from a control series, the subsequent course of the 18 patients with coexistent tuberculosis and fungus disease was more rapidly downhill and the mortality appreciably greater. The question arose as to whether there was some symbiotic relationship to explain the greater mortality in the smaller group. At this time, the question has never been adequately answered.

The author has striven, during the compilation of this book, to include present-day information of scientific import on the technological aspects of systemic fungus diseases associated with pulmonary pathology. Thousands of actual case reports have been reviewed in order that an independent viewpoint might be obtained on the pertinent information from the initial sources, that is, from individual case reports. Whenever possible, this information has been documented by abstracting the clinical findings in each case. As far as feasible, direct quotations from available texts have been reduced to the minimum. In short, a clinicopathological investigation has been compiled to that end, in the hope of amplification or substantiation of previously expressed opinions on the subject of systemic fungus diseases.

The forgotten host, the individual who is afflicted with the disease, has not been ignored. The values of the findings of the mycologist, pathologist, immunologist, roentgenologist, epidemiologist, statistician, and the basic researcher are all realized. Their contribution is essential and definitely necessary. All too often, the affected one, the patient, is overlooked. "The patient is sick all over" is a truism, sometimes neglected in the mental fog that is caused by a unilateral approach to the clinician's problem.

Disease varies tremendously, and much of this variability depends upon the soil on which the incitant becomes engrafted. Furthermore, the patient's individual presenting complaints, as expressed by him, constitute the very beginning of the awareness of illness. It takes a great deal of training and experience for the clinician to decide which of the patient's complaints are significant. It cannot be overstated that these facts, as expressed by the patient, are extremely important, because they encourage the physician to investigate the possibility of fungus disease.

Considerable space, therefore, has been allotted to the clinical symptomatology, in addition to more scientific mycological aspects. There must be a close and intimate association between the pathologist and the clinician, for the ultimate diagnosis and differential diagnosis must be made by the former. It is true, however, that astute judgment by the clinician is important in initiation of the preliminary investigation, and, when all the factors have been assayed, in correct diagnosis. Clinical acumen is also essential in the subsequent labors to ameliorate the patient's condition or to bring about a cure of his affliction.

ACKNOWLEDGMENTS

The author could not have consummated the commission to complete the task of reviewing the extensive literature of the past twenty-five years, dealing with systemic fungus diseases of the lungs, and preparing this treatise, without the assistance of many of his colleagues within the Western Hemisphere. A great amount of subject matter has been generously supplied to me. They have been so liberal the author has had some difficulty in absorbing all of this material within the dimensions of this book. Such magnanimity toward the author confirms the premise that understanding and helpfulness among physicians are not confined within geographical boundaries.

My personal expressions of gratitude to all who have assisted me does not adequately impart my sense of obligation toward my conferees. The following physicians were especially helpful: Jose Ignacio Baldo, J. W. Birsner, E. W. Chick, Norman F. Conant, W. W. Coulter, Sr., Marcus L. Dillon, Eduardo Etzel, J. H. Smith Foushee, Charles Friedman, M. L. Furcolow, C. Allen Good, Paul R. Hausmann, Felix A. Hughes, Jr., Robert W. Huntington, Jr., Lewis G. Jacobs, Victor A. Kelmensen, Alton Ochsner, Arthur M. Olsen, John K. Poppe, James V. Rogers, Jr., Herschel Sidransky, B. H. Webster, and Lyle A. Weed.

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A.E.G.

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