AN
INTERNATIONAL
SYMPOSIUM

THERAPY
OF
Fungus
Diseases

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THERAPY OF FUNGUS DISEASES

An International Symposium

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PRESENTED JUNE 23, 24, 25, 1955, BY

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LITTLE, BROWN AND COMPANY
BOSTON · TORONTO

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LIBRARY OF CONGRESS CATALOG CARD NO. 55-11816

FIRST EDITION

Published simultaneously in Canada
by Little, Brown & Company (Canada) Limited.
Published in Great Britain by J. & A. Churchill, Ltd., London.

PRINTED IN THE UNITED STATES OF AMERICA

Foreword

The symposium reported in this volume was organized for the purpose of stimulating an exchange of ideas on both a national and an international level concerning the therapy of fungus infections. It was held under the auspices of the Division of Dermatology, Department of Medicine, School of Medicine and Medical Extension, University Extension, University of California at Los Angeles.

It is our feeling that the symposium was successful in achieving its primary purpose. A total of 208 scientists participated, representing 24 states and 8 foreign countries. In addition to the papers presented, an important aspect of the symposium was the establishment of personal contact among many of the participants who previously had known each other only by name. It was necessary to limit the length of the papers in this publication because of the large number presented, and therefore the majority are condensations of the material given at the symposium. For similar reasons it was not feasible to include any of the discussions which contributed so much to the over-all interest of the program. In an effort to expedite publication, reproduction of tables and charts was done by photographic process wherever feasible.

This symposium was made possible by the financial assistance of the Squibb Institute for Medical Research. To a large extent, the success of the symposium was due to the care with which the Planning Committee (Drs. Roger O. Egeberg, William L. Hewitt, David L. McVickar, Orda A. Plunkett, J. Walter Wilson, and Edwin T. Wright) formulated the program. The smoothness with which each session proceeded attested to the skill of the chairmen: Drs. Harvey Blank, Norman F. Conant, Arthur C. Curtis, Chester W. Emmons, and Donald M. Pillsbury. The efficiency of the symposium operation as a whole was due to the planning and hard work of the Medical Extension Staff: Gertrude H. McSpedden,

Susie Cartt, Vivian Omerberg, Patricia Martin, and Macine Lustig. We wish also to thank Ronald M. Reisner for his contribution in the editing of this volume. Finally, we should like to express our appreciation to the staff of Little, Brown and Company for making possible the early publication of the material.

Thomas H. Sternberg, M.D., Chairman
Victor D. Newcomer, M.D., Co-chairman

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Introductory Remarks by Donald M. Pillsbury

It is perhaps improper for someone who is not primarily a mycologist to attempt to introduce this symposium on the therapy of fungus diseases. Nevertheless, any clinician who must be responsible for the treatment of patients suffering from superficial or deep fungus infections is all too keenly conscious of the general lack of specific and effective methods of dealing with such diseases. Among all the microbial infections of man, the diseases caused by fungi are perhaps the most difficult to modify in their course, or to prevent. The conquest of most bacterial infections is well known — though the tide of battle may turn against us if we continue to use antibacterial agencies with the profligacy with which they have been employed to date, with the resultant emergence of resistant bacterial strains at a rate which is more rapid than that at which microbiologists and chemists can develop new antibiotics. The Rickettsial and Chlamydozoaecae infections are one by one yielding either to chemotherapy, or to prophylactic immunization. Viral infections, though not influenced by any specific methods of treatment, can in some instances be completely prevented by immunization. In the case of diseases caused by the superficial ringworm fungi, on the other hand, the methods of treatment are generally roundabout and non-specific. The modes of transmission of all except tinea capitis are relatively unknown and subject to much speculation; and the available methods of prevention are poor. In only two of the deep fungus infections, blastomycosis and sporotrichosis, are the methods of treatment reasonably satisfactory, and even in these there is room for much improvement. There are no practical methods of immunization against any fungus infection.

One of the best indices of the clinical importance of a particular group of diseases, and of the dissatisfaction with available methods of controlling them, may be found in the interest and concern shown by agencies which have a responsibility for the health of large groups of people. I have participated in the deliberations of several of these agencies in respect to fungus infections, and would like to cite some of this experience briefly.

The experience of the armed forces with fungus infections during the war was most discouraging, and the situation has improved but little since. A major portion of the dermatologic disability during the war resulted from superficial ringworm infections, or conditions which were misdiagnosed as such. It was clearly apparent that the training of American physicians and laboratory workers in the diagnosis of superficial ringworm infections was inadequate. Any inflammatory eruption which occurred on the feet or groin, or any scaling dermatosis which produced ring-shaped lesions, was almost automatically diagnosed as a fungus infection. At the beginning of the war, there was great official confusion as to the preferable methods of prevention and treatment. This was to some extent resolved, after much discussion, by the wide-scale introduction of fatty acid preparations for prophylaxis and therapy. Although these preparations are known to be very feebly antifungal *in vivo,* and rarely capable of curing a superficial ringworm infection, they possess the great advantage of being almost completely non-sensitizing, and relatively non-irritating. The situation in respect to preventive measures was equally confused, and a variety of powders and footbaths were variously employed. Eventually it was agreed that prophylactic footbaths were useless, if not actually harmful at times, and that prevention was best achieved by foot hygiene which was as scrupulous as possible, without resort to antifungal agents. Since the war, the problem of superficial ringworm infections has required continuing attention by the armed forces.

Another disease from fungus infection, namely coccidioidomycosis, became a major disease problem during the war. The units principally affected were armored forces which had trained in areas in which coccidioidomycosis was endemic. This problem is well known to all physicians in California, but the numerous instances of progressive coccidioidomycosis which were encountered

later represented a new and unusual experience to many medical officers. There was absolutely nothing that could have been done about this, either from the standpoint of prevention or treatment, a situation which obtains to this day.

In addition to the armed forces, the Institute of Microbiology of the National Institutes of Health has long been keenly aware of fungus infections as a significant public health problem, and of the great need for fundamental studies in this field. However, investigations of other more spectacular diseases have gained the support of the public and the Congress, and it has not been possible to stimulate and support such studies as fully as is desirable. Furthermore, there are not many laboratory scientists who are competent mycologists, and the number of proposals for studies along sound and original lines has been small to date. Within the past few months, this problem was considered at length by an *ad hoc* committee summoned at the instance of Dr. Leonard Karel, Chief, Extramural Programs, National Microbiological Institute. It is hoped that, eventually, a larger number of fundamental studies in the field of mycology can be stimulated, and that support for them will be forthcoming.

The program of this symposium contains many titles which excite one's interest. In the following brief remarks on what might be done to remedy the present situation, I shall no doubt include something which has already been done, and which will be reported during the next two or three days. As one surveys the published reports dealing with laboratory or clinical studies of the mycoses, the impression mounts that too many investigators are simply treading water in a very small and restricted pond. Several examples of this may be cited. There are myriads of reports dealing with the botanical characteristics of the growth of fungi *in vitro* on various artificial media, and they continue to appear. Familiarity with this discipline is essential to anyone who proposes to study mycologic diseases, but as an end of and by itself, it is unpromising. There has been, and is, excessive preoccupation with the development of compounds for the topical treatment of superficial ringworm infections. This cannot be expected to subside completely, because the phenomenon of a pathogenic organism growing on the very surface of the skin, in a position where topical therapy might fully be expected to be effective, offers a

therapeutic challenge which can hardly be resisted. It would also appear that there may have been excessive preoccupation with studies having to do with the recovery of fungi from diseased tissue, particularly skin, without sufficient emphasis upon determining whether or not the fungus is contributing to the disease process in question and if so, to what extent. Possibly the best examples of this are the numerous studies having to do with the recovery of Candida from the normal and abnormal skin, mucous membranes, and viscera, with no certain means of determining whether the condition should be labeled moniliasis or if the Candida present should be regarded only as fortuitous saprophytes.

It is my belief that the investigative approaches to the therapy of fungus diseases must be increasingly bold and imaginative. This necessarily will involve basic studies which do not — indeed should not — have any prospect of immediate practical application. In the following paragraphs, I have attempted to list a few examples of approaches which appear worthwhile.

What are the modes of transmission and the natural reservoirs of pathogenic fungi? The natural reservoirs of organisms capable of producing deep fungus infections offer a fascinating and important field of study. In the case of a disease such as coccidioidomycosis, the available knowledge of the natural reservoirs of the fungus has proved to have great practical usefulness, though those working in the field are, I am sure, still dissatisfied with their knowledge of this problem. All of the other deep fungus infections furnish similarly inviting fields of study. As to reservoirs for the transmission of superficial ringworm fungi, there is a lack of firm knowledge which is truly astonishing. Something, though not enough, is known in regard to the contagiousness of tinea capitis. Knowledge in respect to the ringworm fungi affecting the glabrous skin is extraordinarily nebulous. It has long been assumed that the fungi which are associated with dermatophytosis of the feet are transmitted through showers, bathroom floors, swimming pools, and so on. Yet when these supposed sources of infection are painstakingly and scrupulously searched for pathogenic fungi, they rarely yield any, and then only a few organisms. Familial transmissions of such infections are almost unknown in temperate zones. Attempts to produce athlete's foot in man, under what might be regarded as optimal conditions, meet with either failure,

or a short-lived inflammatory reaction which is in no respect comparable to the natural disease. All this constitutes a fascinating mystery, on which little light has as yet been shed.

Why are the superficial ringworm fungi necrophilic? As has been shown by many observers, particularly in the series of studies by Kligman,* the superficial ringworm fungi lack the capacity to invade living tissue. When they invade the scalp and the shaft of the hair, they progress downward along the hair shaft only to the layer of parakeratotic cells, and no farther. On the smooth skin they can be demonstrated only in the stratum corneum, never in the underlying living epidermal cells, except in decadent and dying form in Majocchi's granuloma. There is, indubitably, something in the living cell which completely stops the further growth of these organisms. What is it?

What are the precise nutritional requirements for the growth of pathogenic fungi? In developing laboratory procedures to make a diagnosis of a fungus infection, the efforts of most investigators have been directed toward providing a nutrient substrate which will furnish the best possible growth conditions for the fungus *in vitro*. Much is known as to the varying characteristics of fungus growth with different types of media, but the precise reasons for these are little understood. This furnishes another inviting field of study, but one which probably cannot be prosecuted adequately on the basis of ordinary botanical mycology, but will require the techniques of enzymology and cytology. The growth requirements of the pathogenic fungi have not received anything approaching the study which has been given to bacteria in recent years, nor are the precise cytologic changes under varying conditions as well established.

How do the superficial ringworm fungi produce their harmful effects? In many diseases of the skin and mucous membranes, the recovery of a particular strain of fungus from the affected area still leaves the clinician in a quandary as to whether or not the fungus is causing the disease in question. With many of the deep fungus infections, there can be no question that the disease state is largely produced by the invader. In some superficial infections (for example, tinea capitis, or chronic *Trychophyton rubrum*

* Kligman, A. M. Tinea capitis due to *M. audouini* and *M. canis*. A.M.A. Archives of Dermatology 71:313, 1955.

infections, or vesicular and bullous eruptions associated with *T. mentagrophytes*) there can be little doubt that the pathologic changes seen are due primarily to the fungus present, though the precise disturbances in host-parasite relationship may not be fully delineated. Under other circumstances, the role of the fungus becomes less certain. This is seen in many chronic intertriginous eruptions of the feet, from which a fungus may be isolated, but in which other factors seem to be principally responsible for the inflammatory changes. The situation in respect to Candida infections is even more uncertain. This organism may be recovered from a wide variety of lesions of the skin and mucous membranes, and from viscera as well, but it is extraordinarily difficult to determine the degree to which it is contributing to the inflammatory changes seen, if, indeed, it is contributing at all. It is fashionable to regard many of the reactions to broad-spectrum antibiotics as due to the addition of Candida to the microflora of the skin and mucous membranes, but this may be regarded as highly uncertain, as a rule.

Why is topical therapy for the superficial mycoses so ineffective? As mentioned previously, the general lack of specific chemotherapeutic antifungal compounds is nowhere better illustrated than in the diseases caused by the ringworm fungi. There are, I suspect, few large pharmaceutical houses in the world where the synthesis and testing of agents designed for the topical treatment of the superficial mycoses is not being pursued. One suspects that such studies are foredoomed to failure, though this is a rash statement. In any event, they should be preceded by a better understanding of the penetration of fungicidal or fungistatic agents into the keratinous dead cells of the stratum corneum, hair, and nails. Much more needs to be learned of the mechanisms by which fungi produce inflammatory changes. Along with many others who have suffered disappointments in the clinical trials of such topical agents, I suspect that the eventual curative agent will be administered systemically, and will be something which will concentrate and persist in the epidermal cells. However, significant progress has been made in the development of antifungal antibiotics, and one may indulge some hope that these, like antibacterial agents, will have curative effects when applied topically to superficial ringworm infections.

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What are the host-parasite relationships? Fungus infections present an array of questions in relation to age and sex incidence, and variability of course, which constantly puzzle the clinician. Why do some types of tinea capitis affect only children, while others affect adults as well? Why are fungus infections of the feet seen with such rarity in children, so uncommonly in adult females and so commonly in adult males? Why is coccidioidomycosis a benign self-limited disease in some individuals, and a progressive lethal one in others? Why does this infection become disseminated so much more commonly among Negroes than among whites? Why is histoplasmosis, a common deep fungus infection in some regions, productive of clinical signs in only a few of the individuals affected? Questions such as these might be listed almost indefinitely, and, admittedly, they might be asked in respect to many bacterial and other infections concerning which we profess to know a great deal more than is the case with fungus infections.

These random remarks have been made to give some indication of the extent and importance of fungus infections as a source of banal, disabling, or fatal disease in man, and to cite a few examples of the fascinating array of investigative approaches which present themselves. I am sure that all of us in this group, which contains representatives from many lands, are fully in accord with the need for a discussion of these matters, and are most appreciative to the Medical School of the University of California at Los Angeles for arranging this symposium, and to E. R. Squibb and Sons for supporting it.

June 23, 1955

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