Occupational Mycoses

Edited by Arthur F. DiSalvo, M.D.

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Lea & Febiger • Philadelphia • 1983

Lea & Febiger
600 Washington Square
Philadelphia, PA 19106
U.S.A.

Library of Congress Cataloging in Publication Data
Main entry under title:

Occupational mycoses.

Bibliography: p.
Includes index.
1. Mycoses. 2. Occupational diseases. I. DiSalvo, Arthur F. [DNLM: 1. Mycoses. 2. Occupational diseases. WC 450 015]
RC117.023 1983 616.9'69 83-765
ISBN 0-8121-0885-X

PRINTED IN THE UNITED STATES OF AMERICA

Print No. 3 2 1

FOREWORD

The field of occupational health has developed rapidly during the last few years, and occupational health professionals are now involved with a broader variety of workplaces located in many different communities, sometimes in several nations. Occupational health professionals, whose attention was once largely focused on manufacturing and extractive industries, now accept the importance of recognizing and controlling occupational health problems in construction, forestry products, agriculture, retail trade, high technology, and service industries. These changes and changes in the workforce increase the need for occupational health professionals to enhance their understanding of fungal infections. An aging workforce, widespread use of medications to control a variety of chronic diseases, medications or disorders affecting immunocompetence, and equal employment opportunity requirements are factors that may affect susceptibility to fungal infections. In meeting their extended responsibilities, occupational health professionals can be expected to encounter questions relating to the occupational mycoses. In the future, questions regarding the work-relatedness of fungal infections are likely to be encountered more frequently in worker compensation and product liability cases. Textbooks in occupational medicine and industrial hygiene in general have not provided much information about fungal infections.

It is hoped that this book will serve as a guide to assist health professionals in the recognition of environmental hazards and proper placement of workers with known susceptibilities, as well as in the early recognition and improved treatment of occupational mycoses. In so doing, one can hopefully help contain worker compensation and product liability costs related to the occupational mycoses.

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PREFACE

Textbooks of medicine, in general, present only brief discussions of fungal infections. On the other hand, textbooks of medical mycology describe the protean manifestations of mycotic infections in great detail with extensive discussions of their etiologic agents. The purpose of this book is to provide clinical and epidemiologic information specifically relevant to those mycotic infections which may be acquired at the work place. It is intended for physicians and nurses in occupational medicine, industrial hygienists, internists in infectious or pulmonary disease, dermatologists, pathologists, mycologists, epidemiologists, and all others concerned with occupational health.

As stated by Dr. John F. Finklea, former Director of the National Institute of Occupational Safety and Health ". . . although the history of occupational diseases extends back for centuries, many of them still go unrecognized today."[4] Indeed, occupational medicine has had a long history. In 1556, Georgius Agricola published "De Re Metallica" in which he described the industrial hazards of dust in mines. In 1700, Bernardino Ramazzini, the "Father" of occupational medicine, published "De Morbis Artificum Diatriba" which is considered to be the seminal work in this discipline. During the last 300 years, many diseases have been related to occupation. The jeopardy of exposure to carcinogens and other toxic substances at the work place has been recognized only in recent years. Now the potential biohazards of pathogenic fungi in work settings are beginning to be described.

Because many mycotic diseases have a prolonged period of evolution, the physician should carefully question the patient regarding past work history in addition to present occupation. The occupational physican should also consider the recreational activities and hobbies of the patient. An awareness of the ecologic associations of the pathogenic fungi and the clinical manifestations of the diseases they cause should lead the industrial physician to consider the mycoses in the differential diagnosis of a patient's illness. Indeed, this is the only way by which new occupational diseases will be recognized. This approach may even uncover new ecologic associations for pathogenic fungi.

Several factors must be considered in order to establish a relationship between disease and occupation. For many diseases, it may be difficult or impossible to prove such an association. For example, heart disease, hearing loss, or arthritis may be due to employment factors or to many nonoccupational factors. In mycotic diseases, however, the isolation of a pathogenic fungus from a work area may be strong evidence of an association between the patient's disease and the point source of the mycotic agent. In some mycotic diseases, such as aspergillosis, the linking factor may be isolation of a particular species of the genus *Aspergillus;* although in other mycotic diseases, such as fungal hypersensitivity, the mere isolation of the saprophytic molds usually associated with this clinical entity may not be sufficient evidence to establish a causal relationship.

Several factors should be considered in diagnosing an illness in a patient as an occupational mycosis. First, the questions should be asked: Is the patient's disease indeed a mycotic infection? Are the clinical signs, symptoms, and course of illness compatible with the usual manifestations of the disease? The physical examination should be compatible with the disease entity, and laboratory evidence should support the diagnosis based, for example, on radiographs, serologic tests, skin tests, or histologic examination of biopsy or autopsy specimens. Finally, has the etiologic agent been isolated from appropriate clinical material?

A second factor critical to establishing the occupational association of the mycotic agent is the isolation of the organism from the work environment. With some fungi, additional common factors between the patient's isolate and the environmental isolate would be required, such as the same species (dermatophytes, Chapter 9; aspergillosis, Chapter 8), the same serotype (cryptococcosis, Chapter 1), or some other distinguishing characteristics (mycotic hypersensitivity, Chapter 11).

A third factor to consider is whether an opportunity existed for the patient to become infected at the work site. Such exposures, for example, could be a break in laboratory technique, the unexpected creation of an aerosol, a laceration or abrasion of the skin, or a lack of appropriate protection devices (Chapter 13).

Finally, nonoccupational exposure, such as in recreational pursuits, must be considered. The increase in recreational activities in the United States, particularly in outdoor activities, is well known. As will be discussed in the following chapters, most pathogenic fungi are saprophytes in nature, and many outdoor pursuits place the individual in intimate contact with these fungi in their natural habitats.

Chapters 1 through 10 are devoted to specific mycotic infections and present basic information on the etiologic agents and their known ecologic associations. This material is provided so that the attending physician will correlate these data with the known occupational history of the patient. The most effective and specific diagnostic tests for the mycotic diseases are also presented. The ones listed are not presented as mandatory or complete because the diagnosis of the mycoses is in a dynamic state. New methodology, for example, has aided in the development of more specific antigens for skin testing (spherulin) and for serologic tests (immunodiffusion).

Chapters 11 and 12 on mycotic hypersensitivity and pulmonary mycotoxicosis present a clear, concise description and distinction between two noninfectious disease entities caused by fungi and thermal-tolerant actinomyces. These illnesses are almost exclusively occupationally oriented.

Chapter 13 describes a work place where infectious mycotic agents present a potentially serious hazard—the diagnostic or research laboratory. The employees in this worksite are at risk to the greatest variety of fungal pathogens. During the past 25 years, laboratory accidents have received increased attention.

The majority of fungal pathogens are basically saprophytic organisms that are ubiquitous in nature even when limited to a particular ecologic niche. The whole world cannot be made safe from these biohazards; however, specific loci such as playgrounds, parks, buildings about to undergo renovations, and other autochthonous nidi of infectious agents that are used by man or are about to be disturbed by man (anthropurgic activities) and that have been demonstrated to harbor these pathogenic fungi can be rendered relatively nonhazardous by certain disinfection techniques. These practical methods are outlined in Chapter 14 with descriptions of the latest technology available to prevent occupational exposures where the sites are in active use.

The National Morbidity Reporting System compiles morbidity reports in the United States through the Epidemiology Program Office of the Centers for Disease Control (CDC), Atlanta, Georgia. Although mycotic diseases are not notifiable, i.e., the physician is not required to notify local health authorities of each occurrence of the disease, they are optionally reported by some States. Any mycosis reported by a physician will usually be compiled by the CDC in its annual list of optionally reported diseases. Only when the majority of physicians report their cases will we begin to measure "the portion of the iceberg which rests below the surface of the sea of mycological ignorance.[1]"

The latest available annual summary of the Reported Morbidity and Mortality in the United States was prepared in 1980 and presents the data for 1979. The table of deaths from nonnotifiable acute diseases during the 10-year period 1969 to 1978 shows that the number of deaths due to fungal infections rose from 405 to 635, an increase of 57%. Whether this represents increased incidence or greater recognition due to improved diagnostic acumen cannot be determined at this time.

Many fungal diseases are related to occupations; e.g., sporotrichosis occurs among florists, gardeners, forestry workers, and brick layers; chromomycosis frequently develops in agricultural workers and farmers; veterinarians are commonly infected by zoophilic dermatophytes; and coccidioidomycosis has among its victims archaeologists, tourists, and operators of earth-moving equipment. Histoplasmosis is common in heavy-equipment operators, speleologists, and construction workers involved in demolition of buildings. Cryptococcosis may also be an occupational hazard for those involved in the demolition of old buildings. Of the several books on occupational disease I have reviewed, only two mentioned mycotic diseases. One, a publication by the National Institute of Occupational Safety and Health, devotes only eight of its 600 pages to the subject.[4] The other entitled Occupational Mycotic Diseases of the Lung, published in Budapest, Hungary in 1968,[3] described infectious mycotic diseases in 50 pages, various toxins in the next 85 pages, and respiratory diseases caused by plant fibers in the last 30 pages.

The concept of regional endemicity of mycotic diseases should be discouraged. This idea has usually been interpreted to mean that some mycoses do not occur in other areas of the world and is one reason why physicians have not frequently considered mycotic diseases in the differential diagnosis. Although some specific pathogenic fungi may have their ecologic niche in certain geographic areas, the distribution of pathogenic fungi is certainly much greater than was once thought. Mycotic diseases are apparently more widely distributed because of the transient nature of today's population, the voluminous international shipment of raw materials and finished products, and the discovery that natural nidi of mycotic agents occur in a wider range than formerly believed. In addition, the natural airborne transmission of infectious particles for many miles must be considered. This was illustrated by the distribution of *Coccidioides immitis* spores by a dust storm from Bakersfield to northern California in December 1978 (Chapter 2).

Mycologists themselves may be responsible for the failure of diagnosticians to consider mycotic diseases in their differential diagnoses, because they propagate the concept of the limited geographic distribution of these organisms. The patient–physician encounter may occur far from the ecologic niche of the fungal pathogen and many years subsequent to the exposure.

The terms "North American blastomycosis" and "South American blastomycosis" add to this regional concept. These terms should be abandoned by physicians and replaced with "blastomycosis" and "paracoccidioidomycosis," respectively. Blastomycosis has been reported from Africa and Israel, while paracoccidioidomycosis has been reported from Central America and North America (Mexico) as well as from South America.

This publication is not meant to replace basic medical mycologic textbooks that present the details of fungal morphology, pathology, clinical diagnosis, laboratory diagnosis, or therapy. Information of this type should be sought in such standard textbooks.[2, 5] Sufficient details are given in this text to provide a practitioner of occupational health enough information to understand the occupational mycoses and consider them in the differential diagnosis when a patient presents with appropriate signs and symptoms.

The accurate diagnosis of mycotic diseases is essential not only to the selection of specific therapy for the patient's illness, but also to alert the industry to actual or potential sources of biologic hazards. The occupational mycoses clearly represent a disease entity whose time has come.

Several chapters are based in part on presentations made at the 107th Annual Meeting of the American Public Health Association (Chapters 1, 3, 5, 7, 8, 11, 12, and 13). The symposium "Occupational Mycoses" was presented on November 6, 1979.

REFERENCES

1. Ajello, L.: The Medical Mycological Iceberg. *In* The Epidemiology of Human Mycotic Diseases. Edited by Y. Al-Doory. Springfield, Charles C Thomas, 1975.
2. Emmons, C. W., Binford, C. H., Utz, J. P., and Kwon-Chung, K. J.: Medical Mycology. 3rd Ed. Philadelphia, Lea & Febiger, 1977.
3. Kovats, F., and Bugyi, B.: Occupational Mycotic Diseases of the Lung. Budapest, Hungary, Akademiai Kaido, 1968.
4. National Institute for Occupational Safety and Health. Occupational Diseases—A Guide to Their Recognition. Revised Edition. Washington, D.C., USDHEW PHS, CDC, 1977.
5. Rippon, J.W.: Medical Mycology. 2nd Ed. Philadelphia, W. B. Saunders, 1982.

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CONTENTS

CHAPTER

1

CRYPTOCOCCOSIS

Morris A. Gordon

Cryptococcosis has not been associated with a specific occupation; however, the types of occupation at greatest risk appear to be those in which workers are exposed to large amounts of dust containing organic matter, particularly when derived from dried dung of pigeons or other birds or from soil contaminated with avian excreta.

CLINICAL DESCRIPTION

The presenting symptoms most commonly are those of meningitis—particularly, intermittent and increasingly severe headaches, low-grade fever, and often, disorientation. Pulmonary disease is the second most commonly diagnosed type, although the lungs are undoubtedly the portal of entry for almost all infections. The disease may also disseminate to involve skin, bones, and other organs.

ETIOLOGIC AGENT

The Organism

Cryptococcus neoformans is a spherical-to-oval, budding, yeastlike organism, usually with a conspicuous, mucoid, polysaccharide capsule. It is found in huge numbers in pigeon droppings, to a lesser extent in certain other avian excreta, and in soil contaminated by these materials. Evidence exists that its capsule serves as a virulence factor, inhibiting ingestion of the yeast cell by the macrophage,[5] and it may also account for the extraordinary resistance of the microorganism to desiccation in soil and in bird droppings.[22] *C. neoformans* is the imperfect form of the filamentous basidiomycete *Filobasidiella* *neoformans*,[15] which has been produced in the laboratory by mating experiments, but has yet to be found in nature. The species consists of at least four capsular antigenic types (A, B, C, and D), which differ in relative resistance to cycloheximide and in a few additional physiologic characteristics.[3]

Geographic Distribution

C. neoformans has a worldwide distribution with no known geographic localization, although urban dwellers are much more frequently affected than those from rural areas. For example, of a group of 41 patients with cryptococcosis, 68% worked in the city, in either offices or schools or at home.[12] Capsular antigenic types, however, are differentially distributed. In the United States, among isolates from man and animals, type A is by far the most prevalent, and the relatively few isolates of types B and C have been found mainly in southern California. Type distribution may differ in other parts of the world.[2] All serotypes apparently are equally pathogenic.

Natural Source

The source of cryptococcal infection undoubtedly is inhaled dust laden with *C. neoformans*,[7] and many cases have been associated circumstantially with dried pigeon droppings. Despite the isolation of *C. neoformans* from the crops of a high percentage of the pigeons studied, these birds did not contract cryptococcosis.[25] Interestingly, the microorganism was not recovered from lower parts of the intestinal tract of these same birds.[25] Although *C. neoformans* types A and D have been recovered in abundance from bird droppings and soil and even from air,[24] types B and C have not been found in the environment.[2] The species has been isolated sporadically from other natural sources, including peach juice and contaminated milk.[17] Although epizootics of cryptococcal mastitis have occurred in cattle infected by means of contaminated antibiotics or milking machines, no human cases have been associated with these or with either raw or pasteurized milk (pasteurization kills the yeast). The microorganism has also been isolated from bat guano and from internal organs of these mammals,[13] which suggests that they may be carriers.

Cryptococcosis is noncontagious, and there is little evidence of an endogenous source in man. Only rarely have both geographic and temporal proximity of cases been reported, but in one such instance, 3 cases occurred within 12 months in a small town.[19] Although *C. neoformans* was cultured from various sites in the town, no close association of these cultures with the infected persons could be shown, and pigeons were not incriminated. In a town of about 60,000 people, 11 cases of cryptococcosis (3 pulmonary and 8 meningeal), with 3 deaths, occurred within a period of a few years (4 within 2 months), with onset almost always in the fall (McFarland, R.B., personal communication, 1980). In one of the few instances in which a point source was incriminated,[21] cryptococcosis occurred in 2 boys who had been trapping pigeons in a dusty, abandoned building full of these birds.

INCIDENCE

General Population

Cryptococcosis is an opportunistic disease, occurring predominantly among persons with impaired cellular immunity, especially that caused by Hodgkin's disease, lymphosarcoma, lymphocytic leukemia, or diabetes mellitus, and most particularly in conjunction with steroid therapy. Cases do occur in apparently healthy individuals, however, and often these are associated with massive exposure to certain kinds of dust, thus implying that certain occupations are at greater risk.

Occupational Risks

Organic Dusts

In our experience, apparently healthy individuals who acquired cryptococcosis after exposure to organic dust included men who worked in fertilizer, flour, or textile mills, a seaman who had loaded fertilizer and grain cargoes, and persons who had dwelt or worked in dusty barns, a dusty corn crib, and a dusty toy store. Details of these and additional illustrative cases are given in the discussion of case histories further on in this chapter.

Pigeons and Chickens

There is a curious dearth of pigeon handlers among patients with cryptococcosis, despite immunologic evidence of exposure to the microorganism. In one study, 31% of a group of pigeon breeders showed skin sensitivity to a cryptococcal antigen as compared with 4% in a normal control group.[20] In another study, cryptococcal antibodies were detected by a complement fixation-fluorescent antibody test in 22% of a group of pigeon handlers as compared with 3% of nonhandlers.[27] Cases of cryptococcal infection, however, have been associated with sudden and unaccustomed exposure to pigeons and their debris (three instances are among our illustrative cases) and to chicken manure.

Microbial Cultures

Although microbiology laboratory personnel are exposed to large populations of *C. neoformans,* it is noteworthy that, in a survey of clinical microbiology laboratories,[28] not a single laboratory infection was ascribed to this pathogen. (In contrast, there were 108 cases of coccidioidomycosis, 81 of histoplasmosis, and 8 of blastomycosis). It should be pointed out that *C. neoformans* in the laboratory is generally handled as a moist, yeastlike culture and not in the form of minute, dry particles. If molecular biologists have their recombinant DNA, however, we have our own recombinant *Filobasidiella,* which, with its chains of basidiospores, may yet make cryptococcosis an occupational hazard in the research laboratory.

Sex and Age Distribution

Cryptococcosis occurs in all age groups, but about two thirds of patients are between 30 and 50 years old, and men are more frequently affected than women. Primary pulmonary cryptococcosis reportedly shows a predilection for the white male.[17]

THE OCCUPATIONAL DISEASE

Source of the Organism in the Workplace

The source of the microorganism, as stated earlier, presumably is dust containing organic material, particularly the droppings of pigeons or other birds.

Clinical Aspects

Pulmonary involvement may range from small, asymptomatic subpleural granulomata, through unilateral or bilateral solitary cryptococcomata of various sizes, to massive infiltrates. Symptoms of central nervous system (CNS) cryptococcosis usually develop gradually, with intermittent headaches of increasing severity. Signs of a space-occupying lesion may be present. Papilledema, retinopathy, and optic nerve damage may occur. Dizziness and disorientation are common, and progression of the disease is often marked by mental deterioration. Skin lesions usually are indicative of systemic involvement, but in a number of cases no underlying focus was found. The various manifestations may include papules, acneform pustules, ulcerating subcutaneous abscesses, and eczema. Lesions of the bone are usually osteolytic. Visceral involvement may occur.

Route of Entry

The normal portal of entry appears to be the respiratory system. Among the few reported cases of solitary cutaneous lesions, some may have been primary, that is, resulting from direct inoculation of the skin, but it is also possible that, lacking evidence of external trauma, each of these represented localization of an undetected systemic infection.

Infectious Particles

Whether the inoculum in a spontaneous pulmonary infection consists of a single or a cluster of cryptococcal yeast cells, or of such cells associated with debris, is not known; but, given the relatively large size of the microorganism, the former possibility appears more likely. Evidence exists that a small proportion of the cells of *C. neoformans* found in dried pigeon dung are in the size range of approximately 1 to 2 μm,[22] which is about optimum for human alveolar deposition.