HISTOPLASMOSIS

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JUST 51 years ago at Ancon Hospital in the Canal Zone, Dr. Samuel T. Darling, in one of his studies observed and first described histoplasmosis (*1*). This mycosis, perhaps more than any other, has drawn the attention of the medical world to the importance of fungus infections of man. The discovery was actually a byproduct of a search for another disease. The frequent occurrence of splenomegaly and the known occurrence of cutaneous leishmaniasis in Latin America had suggested to observers that visceral leishmaniasis also might occur in that area. Darling was searching for kala-azar when, on December 7, 1905, examining smears from lungs, spleen, and bone marrow he observed enormous numbers of oval cells 1–4μ in size, situated free or in alveolar epithelial cells. Influenced no doubt by the objectives of his search, he believed the intracellular organisms were flagellate protozoa and he proposed for them the name, *Histoplasma "capsulata,"* the spelling of which he corrected in a later paper.

Darling's Three Cases

The patient was a Martinique Negro admitted to the hospital only 2 days before with a disease which resembled miliary pulmonary tuberculosis. Two other cases came to Darling's attention within the space of 2½ years, and in a second paper (*2*) he repeated almost verbatim his description of the first case and recorded in equally discriminating clinical and pathological detail cases 2 and 3. The second patient, like the first, was a Martinique Negro recently arrived in the isthmus and the third was a Chinese, a native of Canton, who had been in the isthmus for 15 years. Darling found only these 3 cases among 33,000 hospital admissions and concluded that the disease was very infrequent in occurrence. He unsuccessfully sought the etiological agent in surface ground waters and in a wide variety of native animals and insects.

In a third paper published in 1909 (*3*) he again reported the three cases in detail and described histoplasmosis as a fatal infectious disease characterized by splenomegaly, emaciation, irregular pyrexia, leukopenia, and anemia with invasion of endothelial cells in the smaller lymph and blood vessels by enormous numbers of micro-organisms. He described necrosis of the liver, splenomegaly, pseudogranulomata of the lungs and intestines with ulcerations of the latter, and with necrosis of lymph nodes draining injected viscera. Although his concept of the disease included certain errors of interpretation and, being based upon a study of three fatal cases, did not encompass the full gamut of manifestations and degrees of severity recognized today, he drew a surprisingly accurate picture of fatal histoplasmosis.

Darling was convinced by this time that the disease no longer existed in Panama, and he concluded his third paper in almost the same phraseology used in his second with the prophetic statement, "The mode of infection and the portal of entry are unknown; these together

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with the zoological status of the micro-organism may yet be ascertained by physicians living in less salubrious regions of tropical America than Panama and in those not yet disturbed by the sanitarian."

Twenty Years Later

Histoplasmosis did indeed seem to have disappeared from Panama. It was next reported 20 years later and 3,000 miles away in Minnesota (*4*), but under what degree of neglect on the part of the sanitarian we are not told. It reappeared also in the tropics in 1926 with the fifth report of a fatal case in a Honduran laborer on a banana plantation (*5*). Although the next report actually from the isthmus was that of a canine case reported by Tomlinson and Grocott in 1945 (*6*), it is now apparent that histoplasmosis is of frequent occurrence in Panama and undoubtedly there has been no interruption in its occurrence as a common but inapparent disease in this area. The evidence from skin tests (*7*, *8*) and soil isolations (*9*) in Panama supports this concept.

Actually, the fourth human case of fatal histoplasmosis to be recognized in Panama was reported by Draheim, Mitchell, and Elton (*10*) in 1951, 45 years after Darling's original observations. Recent evidence of human benign infection in Panama comes also from Puckett's very important studies of coin lesions (histoplasmomas) and healed granulomas in which, by special staining, he was able to demonstrate *Histoplasma* (*11*). Nine of the men in his series of 22 had lived 2 years or more in Panama. In an expanded series reported by Forsee, Puckett, and Hagman (*12*), 13 of 30 patients with such lesions had lived in Panama from 2 to 5 years, and there was acceptable evidence that the lesions developed during residence in Panama in 4 of these men.

The 45-year interval between Darling's and Draheim's cases does not reflect a complete disappearance of *Histoplasma* from Panama during that time. Tomlinson and Grocott's canine case reported in 1945 has already been mentioned. An accidental but very important discovery by Zimmerman of a human case of benign histoplasmosis helps to fill in a segment of the history. Reexamination with special stains of a solitary pulmonary lesion in a 4-year-old Panamanian child dying in 1931 with another disease revealed *Histoplasma* in the necrotic center of the healed granuloma (*13*). It may be anticipated that further studies of similar material will yield evidence of additional unrecognized cases of benign histoplasmosis spanning this period when histoplasmosis was overlooked in the country where it was first observed and described.

I am well aware that to this point my historical review of histoplasmosis is familiar, that many severe cases of histoplasmosis have been recognized during the past 2 years in Panama, and that current interest in the mycosis has revealed many as yet unpublished facts about its frequency and importance there.

Status Today

Today histoplasmosis is known in some 22 countries of the world (*14*, *15*), including highly sanitized as well as primitive areas. Histoplasmosis is not exclusively a disease of the tropics or of the United States, where it has been most intensively studied, nor is it a disease of unhygienic geographic areas in the usual connotation of that phrase. Neither is it a protozoan disease, nor a usually fatal disease as Darling supposed, but these are details in the delineation of the mycosis which detract little from the accuracy of its first description and not at all from the genius of the describer.

There have been many steps in the development of our current knowledge of histoplasmosis, but before I review some of these in chronological order, I want to mention another recent significant contribution from Panama. One of the diagnostic problems that benign histoplasmosis has presented is a nonspecific and often minimal host reaction and a paucity of fungus cells in minimal lesions. A histopathological diagnosis, consequently, has often been missed, particularly in old healed lesions where the fungus, presumably, is dead. A number of selective stains have been proposed and used with eminent success, but most of these stain old or dead cells poorly. The most useful stain for the demonstration of *Histoplasma* in old, quiescent and healed lesions is the modification of Gomori's methenamine-silver-nitrate tech-

nique as applied in the laboratories of Gorgas Hospital (formerly Ancon Hospital) and reported by Grocott (*16*). This modification, as he modestly states, does not supplant such stains as the periodic acid-Schiff and the Gridley stains, but it makes cells of *Histoplasma* and other fungi so conspicuous in the section of an old necrotic or partially calcified lesion that their demonstration no longer presents a serious problem.

Discoveries and developments leading to present concepts of histoplasmosis have been reviewed in many papers. Da Rocha-Lima's opinion (*17*), accepted by Darling according to Meleny (*18*), that *Histoplasma* was a fungus was fully verified in 1934 when Tompkins at Vanderbilt University made the first antemortem diagnosis of histoplasmosis by examination of a blood smear (*19*). DeMonbreun isolated in culture and described in great detail the growth of the fungus under varying environmental conditions (*20*). Hansmann and Schencken (*21*) isolated the fungus in the same year, but, because of certain clinical features observed in their patient, they did not immediately reach the diagnosis of histoplasmosis.

Year by year additional cases were reported until in 1945 Parsons and Zarafonetis (*22*) reviewed 71 cases, in only 4 of which the patient had survived to the time of report.

In the meantime an increasing mass of evidence indicated that, in certain geographic areas at least, a pulmonary disease generally assumed to be healed tuberculosis must have some other etiology (*23–25*). Smith (*26*), speaking from his experience with benign pulmonary coccidioidomycosis, suggested this might be a hitherto unrecognized form of histoplasmosis. Christie and Peterson (*27*, *28*) observed an association between histoplasmin sensitivity and the presence of calcified pulmonary lesions in tuberculin negative individuals. Palmer, knowing of these observations, used histoplasmin prepared some time before in the Mycology Unit of the National Institutes of Health (*29*) in his well-known study of tuberculin and histoplasmin sensitivity in student nurses and found remarkable geographic differences in rates of histoplasmin sensitivity (*30–32*).

Furcolow and associates (*33–35*) described the pulmonary lesions and traced the correlation between their development and the acquisition of skin sensitivity to histoplasmin. The nonspecificity of histoplasmin was known before it was used in any mass testing (*29*), and histoplasmin and yeast-phase *Histoplasma* antigens as used today have nonspecific components which limit their usefulness as diagnostic agents in both intradermal and serologic tests (*36–40*). Nevertheless, both uses have resulted in tremendous strides in our knowledge of the frequency of histoplasmosis.

These studies have revealed that histoplasmosis is usually benign, varying in severity from a clinically inapparent respiratory infection manifested only by the acquisition of skin sensitivity to a more severe pulmonary disease with cavitation. Pulmonary calcification is a frequent, but not an invariable, sequela of these mild and moderately severe cases. It is only in the exceptional case that histoplasmosis becomes disseminated and may terminate fatally.

More detailed reviews of the development of our knowledge of histoplasmosis and more extensive bibliographies are given in recent review papers (*41–43*). These papers review also the clinical variations of histoplasmosis, including manifestations not observed by Darling, such as involvement of the central nervous system, adrenal damage, and endocarditis. It is not my intention to dwell further upon the clinical aspects of histoplasmosis since these have been so fully and repeatedly covered in many case reports and review papers.

Laboratory Confirmation

Any reference to the clinical variability of histoplasmosis suggests the importance of a laboratory diagnosis. Laboratory confirmation of a clinical impression or diagnosis is indeed essential in this mycosis. Within limits, diagnostic antigens are useful in attempts to reach a diagnosis. These limitations are perhaps greater than in most bacterial diseases. Dermal sensitivity to histoplasmin persists for many years, and the rate of histoplasmin sensitivity within an endemic area may be so high that a skin reaction has little diagnostic value unless a recent conversion to sensitivity can be

shown. Correlation of rising complement fixation or precipitin titers with an illness has greater diagnostic value than the skin test, but reactions to both histoplasmin and yeast-phase antigens must be interpreted with caution since it is well recognized that several of the pathogenic fungi have one or more antigens in common. Cross reactions with blastomycosis, coccidioidomycosis, or other mycoses may occur in some patients so that it is necessary in a serodiagnosis to obtain paired or multiple serums and to test these against a battery of fungus antigens. Campbell has very ably investigated the problems of the serologic diagnosis of histoplasmosis and has discussed techniques and the correct interpretation of results (*36–38*).

A more conclusive diagnostic procedure is the isolation of *Histoplasma* in culture and this should always be attempted. Sputum, blood, bone marrow, at least in infants, skin lesions, ulcer base, and lymph nodes, or pulmonary lesions obtained by surgical excision, should be spread upon agar slants and incubated at 23°–30° C. Many culture media have been used and their relative efficiency compared, but freshly prepared glucose-neopeptone agar (modified Sabouraud's) is convenient and adequate. When contaminated material such as sputum is used for inoculum, the agar should be made unsuitable for bacterial growth by the addition of 0.5 micrograms each of penicillin and streptomycin per milliliter of agar.

The mouse is highly susceptible to histoplasmosis (*44*, *45*) and may be used for diagnosis by the intraperitoneal injection of sputum. Mice require protection against bacteria in the sputum inoculum, and this usually can be achieved by mixing penicillin and streptomycin with the sputum before injection or by subsequent treatment of the mice. More detailed information about diagnostic procedures is available in many papers.

Epidemiological Features

Histoplasmosis shares with the other deep mycoses an apparent inability to spread from person to person. The parasitic or tissue phase of the dimorphic fungus is infectious experimentally, but it is not an effective agent in transmission of the disease, and contagion of histoplasmosis has not been observed. On the contrary, the patient, according to best evidence available, invariably acquires his infection from an environmental site where *Histoplasma* is growing as a saprophyte.

The infectious particles are the conidia or spores which are produced freely under suitable conditions. They are much more resistant to deleterious influences than the fragile yeast cells of the parasitic growth phase and are inhaled by the patient during the performance of activities which release these spores as airborne dust. This concept rests upon the evidence of many case histories, the demonstration that *Histoplasma* can be grown in the laboratory upon sterilized soil, the isolation of *Histoplasma* in culture from soil in nature, and the actual demonstration of the distinctive macroconidia of *Histoplasma* in soil naturally colonized by the fungus (*46*, *47*).

Since all available evidence had suggested the importance of an environmental source of infection, the Mycology Laboratory of the National Institutes of Health began a systematic search for saprophytic sources of *Histoplasma* in 1946.

Histoplasma was first isolated from soil and reported in 1949 after some 350 specimens had been unsuccessfully examined. Macroconidia were observed in the first positive specimens (*46*). The first positive specimens were two samples of red clay taken from a mound of earth at the entrance to a rat burrow located under the edge of a chickenhouse where infected rats had previously been trapped.

This discovery was made while we were somewhat preoccupied with the possible importance of an animal reservoir and the fact that this, as well as many subsequent isolations of *Histoplasma* were from chickenhouses on farm premises where rats with histoplasmosis had been trapped, obscured at first the more important of the two associations. Zeidberg and coworkers (*48*) were first to point out the association between the saprophytic growth of *Histoplasma* in soil and the presence of chickens. Since this predilection of *Histoplasma* for enriched soil in or near chickenhouses has been recognized, it is now almost routine, within an endemic area, to isolate *Histoplasma* from such sites and often from a high percentage of sam-

ples. Many cases of histoplasmosis in man have been related to exposure to dust, incident to the cleaning of old or neglected chickenhouses. However, such an exposure has not been recognized in many other cases, and *Histoplasma* has been isolated from environments with no apparent relationship to chickens.

It should be recognized further that the frequent occurrence of *Histoplasma* in, under, or near chickenhouses is not dependent upon a host-parasite relationship to the chicken. No naturally infected chickens have been observed, and histoplasmosis cannot be produced experimentally in the chicken although the fungus can be isolated from tissues for a short time after intravenous inoculation. On the contrary this appears to be an entirely saprophytic relationship to enriched soil contaminated by chicken droppings and to other similarly suitable soils with high organic content.

Whether the apparent immunity of the chicken to histoplasmosis is simply a matter of the bird's high body temperature remains to be proved. Mammals, on the other hand, show a wide range of species susceptibility. DeMonbreun (*49*) observed histoplasmosis in the dog, and this animal still represents the only economically important host of histoplasmosis recognized in veterinary medicine (*50*). However, other animals are susceptible. We have isolated *Histoplasma* in culture from 9 other species: the cat, brown rat, roof rat, mouse, fox, opossum, striped skunk, spotted skunk, and marmot (*51*). Others have found the fungus in the horse and cow (*52*, *53*). The histoplasmin skin test has been used widely in veterinary medicine (*54*).

Histoplasmosis, as observed in these animals, has been for the most part a very mild and probably a self-limited disease. We have observed the progressive and fatal form only in the dog although isolation of the fungus from spleen and liver provided evidence of dissemination in many of the cats, rats, skunks, and other animals examined. Our evidence does not show conclusively whether histoplasmosis is a frequent cause of death in wild animals. In the case of dogs and cats, we have conclusive evidence that histoplasmosis usually is benign and that it is an infrequent cause of death. Because of a rabies control program conducted in a rural county in northern Virginia, we were able to get directly from their owners several hundred healthy dogs and cats. Using the most productive method of examination we could devise, the intraperitoneal injection of mice with homogenized hilar and mediastinal lymph nodes, we isolated *Histoplasma* by mouse passage from 50 percent of a series of cats and dogs (*55*, *56*).

Since, in a study extending over a period of several years, we have found relatively few dogs with fatal histoplasmosis, we are forced to the conclusion that most of these healthy animals would have survived their primary infection, in most cases without clinical evidence of disease. We were not able to find a correlation between naturally acquired mild histoplasmosis in the dog, as proved by isolation of *Histoplasma* from lymph nodes, and either dermal or serologic evidence of infection (*56*). This lack of correlation could have been due to inadequacy of the antigens, to the mild and apparently self-limited nature of the disease, or to the varying and unknown duration of the disease in these naturally infected animals. It should be emphasized that, although histoplasmosis occurred in half of the dogs and cats in this particular endemic area, there is no evidence to support the concept that these animals are responsible for the endemicity of the mycosis. On the contrary, as pointed out above, the fungus, *Histoplasma capsulatum* is a part of the saprophytic soil microflora, and it is undoubtedly from this environmental source that both man and animals are infected.

Antibiotic Therapy

There is as yet little to report on the chemotherapy of histoplasmosis. Ascosin and mycostatin (*57*, *58*) can be shown to protect experimentally infected mice against histoplasmosis, but toxicity or inability to attain effective blood levels, or both, have limited the clinical usefulness of these antibiotics. A new antibiotic which shows considerable promise is Amphotericin B (*59*). In experimentally infected mice, Amphotericin B will not only protect mice from death but will clear the tissues of fungi as indicated by negative cultures when

the experiment is terminated. Clinical experience with this antibiotic is still limited.

The number of publications on histoplasmosis now appearing annually is many times greater than all the medical literature on all the deep mycoses published during the 3 years while Darling was searching for what he believed to be a new type of leishmaniasis. Many of the questions concerning the etiology and epidemiology of histoplasmosis left unanswered by Darling have now been answered, but we still seek information about its geographic endemicity, its clinical variability, and, especially, its safe and effective treatment. It is appropriate that during recent years attention has again turned to the part of tropical America which, in a sense, was the cradle of histoplasmosis. The concerted attack upon histoplasmosis now anticipated here will surely be productive.

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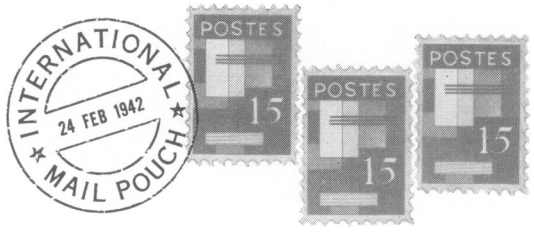

Passing of a Practice

When three Chinese experts, a WHO adviser, and a sanitary engineer arrived in Japan from Taiwan for a 2-week tour of inspection, they found that more than a hundred cities were building sewer or sewage treatment systems. The team took for granted that this building was spurred by a desire to make night soil fertilization safe for public health. But they discovered that the Japanese Government had no program encouraging the use of night soil, although 2 systems for night soil treatment and 1 garbage composting plant are under construction. The death knell of this controversial, age-old practice was sounded by the progress of industrialization and education of farmers, by broadened access to chemical fertilizers, and by the modern policies of the Ministry of Health and Welfare, which were accepted by the Ministry of Agriculture.

—JOEL I. CONNELLY *and* A. DALE SWISHER, *engineers, United States Operations Mission, Taiwan.*

Anthrax Factories

Although Iran is not a highly industrialized country, industrial labor forms a noteworthy proportion of the population. Except for a few organizations such as the National Oil Company, management pays little heed to health requirements of the workers.

Recent reports on the prevalence of anthrax in some of the wool and hide factories caused us to have health conditions inspected. The health department physician assigned to the task reported that plant managers do not consider health matters of importance. The factory environment generally is insanitary. Some factories are without windows; the air is often foul and in most full of dust. Satisfactory lavatories are lacking in many plants.

—GLEN W. MCDONALD, M.D., M.P.H., *chief, Public Health Division, United States Operations Mission, Iran.*

A Day to Remember

Not one villager in a hundred in Alamata, Ethiopia, had seen a movie before we scheduled a film show on malaria, in advance of operations to be carried out in the Kobo-Chercher plain, north of Addis Ababa. For electrical power for the movie, we carried a generator in our big truck, locally dubbed the "kudu wagon."

An hour before dark, the villagers began to gather around the projectors set up in the market place. The governor and head men, including invited guests from neighboring villages, arrived at dark and were ushered to the few available chairs.

As the first film strips were shown, the audience of 500 swelled to 800. They were all eyes and ears! Next on the program was a malaria movie, explained by an Ethiopian official speaking Amaric. Last, a film showed the Emperor on his 1954 visit to the United States. The response, Ethiopian team members assured us, meant that the villagers now had a new understanding of malaria and of what the strangers from America, working with their fellow countrymen, were trying to do.

—PAUL L. RICE, *entomologist, United States Operations Mission, Ethiopia*