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Comparative Ecology of Respiratory Mycotic Disease Agents[1]

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INTRODUCTION

In recent decades, much knowledge has been accumulated concerning the pulmonary mycoses. The signs, symptoms, and the clinical course of these diseases have been defined, and adequate laboratory diagnostic techniques involving both cultural and serological procedures have been perfected. With the discovery of amphotericin B, a significant breakthrough has been achieved in the therapy of the pulmonary mycoses, and one can anticipate the introduction of new and improved therapeutic procedures.

Taxonomic studies of the fungi that cause pulmonary diseases have resolved the most urgent problems of classification and identification. Through biochemical and physiological investigations, an insight has been gained into the metabolic processes of these fungi.

Epidemiological studies have also been productive. The source of infections and the means by which they are acquired and disseminated are rather well defined in most instances. Promising advances have been made in the development of control measures.

In contrast, knowledge regarding the ecology of these fungi, i.e., the study of their relationship to their environment, is rather superficial and scanty. This is so true that it might appear premature and pretentious to discuss the comparative ecology of the agents that cause respiratory mycotic infections. However, a critical review of the current status of all available information was considered to be well worth undertaking. It should serve to bring together data that are widely scattered, enable us to scrutinize critically the information, point to areas of ignorance, and, we hope, inspire others, especially well-trained ecologists, to carry out studies with the breadth and depth that the science of ecology requires.

For practical reasons, species of fungi that are rarely, if ever, encountered as primary disease agents have been excluded from this discussion of the comparative ecology of the fungi that cause pulmonary diseases. They generally come to

[1] A contribution to the Round Table on Respiratory Mycoses: Comparative Epidemiology, Ecology, and Immunology, presented at the Annual Meeting of the American Society for Microbiology, Los Angeles, Calif., 3 May 1966, with Roger O. Egeberg as convener.

TABLE 1. *Isolation dates of respiratory mycotic agents*

Pathogen	Date	Investigator	Ref.
Blastomyces dermatitidis	1898	Gilchrist and Stokes	89
Coccidioides immitis	1900	Ophüls and Moffitt	162
Cryptococcus neoformans	1894	San Felice	181
Histoplasma capsulatum	1934	De Monbreun	51

medical attention as secondary invaders in chronic, debilitating diseases such as cancer, diabetes mellitus, and tuberculosis, or when chemotherapeutic and immunorepressive measures, undertaken for the control of bacterial diseases or neoplasms, interfere with the patient's defense mechanisms. Accordingly, we will not take up such organisms as *Aspergillus fumigatus*, *Candida albicans*, *Geotrichum candidum*, and various species of zygomycetes.

We will discuss only those fungi that are almost invariably primary pathogens and that are most frequently encountered as pulmonary disease agents. These species are: *Blastomyces dermatitidis*, *Coccidioides immitis*, *Cryptococcus neoformans*, and *Histoplasma capsulatum*.

BACKGROUND

All of the fungi under discussion are exogenous parasites, since they are not normally harbored by humans and lower animals. They are known to exist or, in the case of *Blastomyces dermatitidis*, are presumed to occur in nature as free-living saprophytes. They differ from the overwhelming majority of saprophytic fungi in their highly specialized ability to survive, multiply, and cause disease once they have entered the body of a susceptible mammalian host. Whatever knowledge we possess regarding their relationship to the environment is of relatively recent origin. All of these fungi were isolated and cultured for the first time less than 75 years ago (Table 1). Until media and procedures were developed for their isolation and growth in vitro, little could be learned regarding such fundamental facts as their morphology, taxonomy, and physiology.

Speculation regarding their nature, prior to isolation, led to the erroneous supposition that some were protozoans [*C. immitis* (169), *H. capsulatum* (48)]. But, more importantly, ecological studies, primitive as they might be, could not be initiated until the investigator knew what the fungi looked like, grossly and microscopically, in their saprophytic form.

Each of the species will be discussed under the following headings: geographic distribution, prevalence, hosts, and natural habitat.

B. DERMATITIDIS GILCHRIST AND STOKES, 1898

Geographic Distribution

This pathogenic fungus was long thought to be confined to the New World. The very name given to the disease that it causes—North American blastomycosis—implied that it has a restricted geographic distribution. Indeed, the vast majority of reported cases have originated within the United States (34) and in lesser numbers in Canada (96). In both countries, the endemic areas are apparently restricted to their eastern sections.

Various cases reported from Mexico (139), South America (132), Europe (30, 57), and Asia (16, 106, 156) were diagnosed erroneously or occurred in individuals who had contracted their infections in the United States or Canada or were in contact with fomites of North American origin.

Of interest is a case of North American blastomycosis reported from Tunisia by Broc et al. (31) and Haddad (98), with further amplification by Vermeil et al. in 1954 (214). An element of doubt exists concerning the accuracy of the diagnosis in this case. A subculture of the Tunisian isolate (I.P. 268; CDC B-190), kindly furnished by E. Drouhet, Institut Pasteur, Paris, France, in 1957, proved to be nonpathogenic to mice and guinea pigs. In addition, all attempts to convert the organism to a yeast form ended in failure.

However, in 1964 autochthonous cases of indisputable *B. dermatitidis* infections were reported virtually simultaneously from the Republic of the Congo (Leopoldville) (88), from Tanzania, Uganda, and the Republic of South Africa (81, 106), and from Tunisia (55). These African cases reveal that environmental conditions suitable for the growth and survival of *B. dermatitidis* exist not only in Canada and the United States but also on the vast African continent.

The possibility also exists that *B. dermatitidis* occurs in Latin America. Apparently autochthonous cases of infection by this fungus were described from Mexico by Arias Luzardo (19) and from Venezuela in 1954 by Montemayor (154) and by Polo et al. (167).

Thus, our concept regarding the geographic distribution of *B. dermatitidis* must be broadened

TABLE 2. *Annual deaths in the United States due to respiratory mycotic disease agents (1952–1963)*[a]

Disease	1952	1953	1954	1955	1956	1957	1958	1959	1960	1961	1962	1963	12-year avg	12-year total
Blastomycosis	27	23	24	19	27	28	24	13	15	16	17	24	21	257
Coccidioidomycosis	60	85	78	62	54	53	50	48	55	62	55	71	61	733
Cryptococcosis	46	48	56	74	66	55	39	84	71	86	90	73	66	788
Histoplasmosis	51	55	59	53	67	77	73	63	80	90	82	70	68	820
Totals	184	211	217	208	214	213	186	208	221	254	244	238	216	2,598

[a] From Morbidity and Mortality Weekly Report, Communicable Disease Center, Atlanta, Ga. Annual Supplement, vol. 11, 16 September 1963; vol. 13, 30 September 1965.

to meet this new reality. The geographically restrictive term of North American blastomycosis should be dropped, and the disease caused by *B. dermatitidis* should be simply and uncommittedly referred to as blastomycosis. Use of generically derived designations for mycotic diseases is well established in medical mycology. If infections caused by the *Candida species*, *Cryptococcus neoformans*, and *Paracoccidioides brasiliensis* were consistently referred to as candidiasis, cryptococcosis, and paracoccidioidomycosis, respectively, there would be no confusing ambiguities and cause for misunderstanding. In the past, and even today, the term blastomycosis has been used in reference to any infection caused by a yeast. For the sake of clarity such loose use of the term blastomycosis should be ended.

Prevalence—Human

Definitive information on the incidence and prevalence of blastomycosis, as well as all the other mycoses, is lacking. As long as the mycoses remain in the category of non-notifiable diseases, an appreciation of their public health importance, relative to bacterial and viral diseases, will remain nonexistent.

However, there are data available that cast light on the prevalence of blastomycosis. A review by Busey (34) showed that in 170 U.S. Veterans Administration Hospitals, during the period of 1946 through 1957, 198 proven cases of blastomycosis had been diagnosed, an average of 18 cases per year.

In 1955, Schwarz and Goldman (185), through replies to a questionnaire from 1,125 dermatologists and 196 chest surgeons, found that within the United States 99 cases of blastomycosis were undergoing treatment during the first 6 months of 1953. Three of these patients died during that study period.

Statistics on deaths from non-notifiable acute diseases in the United States for 1952–1963 (Table 2) indicate that, in 1953, 23 individuals had died from infections caused by *B. dermatitidis*. The yearly average for the 12-year reporting period was 21, with a grand total of 257.

Canadian records summarized by Grandbois in 1963 (96) revealed that 114 cases of blastomycosis had been reported since Primrose described the first case in 1906 (170). The majority of these cases, 102 (89%), occurred in two provinces: Quebec, 68 (60%), and Ontario, 34 (30%). The remaining 12 (11%) cases had the following distribution: Manitoba, 8; New Brunswick, 2; Nova Scotia, 1; and Saskatchewan, 1.

In a comprehensive review of blastomycosis, Chick et al. (42) plotted the distribution of all reported cases (735) that had occurred within the United States. The states with the highest prevalence of cases either bordered on the Mississippi River or were situated east of that river. The states with 15 or more cases were: Arkansas, 15; Illinois, 74; Indiana, 18; Iowa, 24; Kentucky, 37; Louisiana, 101; Mississippi, 16; Ohio, 38; South Carolina, 90; Tennessee, 90; and Wisconsin, 81.

Prevalence—Lower Animals

It is obvious from the United States data that *B. dermatitidis* infections are prevalent in the human population. Infections in lower animals are also quite common. The dog apparently is the most susceptible of the lower animals. Menges (145) noted that 113 canine cases had been reported within the United States and 3 from Canada. The states with 10 or more cases were: Alabama, 10; Illinois, 21; Iowa, 13; and Kentucky, 27. Later, as the result of an intensive study on canine blastomycosis in Arkansas, a total of 79 cases was credited to that state (152).

The only other known animal victims of *B. dermatitidis* have been a horse in Iowa (24) and a captive Steller's sea lion (*Eumetopsias jubata*) in Illinois (218). Easton (58) reported a case in a Siamese cat. However, on the basis of the infor-

mation presented, the diagnosis is considered doubtful.

Natural Habitat

It is apparent from these data that blastomycosis is not a rare disease and that *B. dermatitidis* must flourish in the environment of the endemic areas. Yet, the natural habitat of this fungus remains elusive. This is stated despite recent reports of the isolation of *B. dermatitidis* from soils in Kentucky and Georgia (53, 54).

Denton and di Salvo's studies raise more questions than they solve. In the Augusta, Ga., area, 10 of 356 soil samples yielded cultures of *B. dermatitidis*. The positive sites included a cattle loading ramp, chicken houses, an abandoned kitchen in a wooden shack, a mule stall, and a rabbit hutch. A correlation between a specific habitat and *B. dermatitidis* could not be drawn. The isolations would seem to indicate, at best, an apparent preference for animal habitats in general, rather than to one specific type.

The study had certain other frustrating aspects. Repeat samples from a site, once found to be positive, consistently turned out to be negative. In addition, with one significant exception. *B. dermatitidis* did not survive for long in the original positive soil samples. After storage of samples at room temperature or in a freezer, (−20 C), *B. dermatitidis* could no longer be recovered from them. The one exception, apparently, was a Kentucky soil specimen that had been collected in a tobacco stripping shed by McDonough (142). It had been stored in a screw-capped glass bottle at room temperature for a least 16 months before *B. dermatitidis* was isolated from it by Denton. Paradoxically, when tested shortly after collection by the original collector, this soil specimen had given negative results (142). As with the other positive soils, despite repeated efforts, the "positive" Kentucky soil never yielded the fungus again. In addition, a large group of new soil specimens collected in the same Kentucky tobacco barn were negative (E. S. McDonough, *personal communication*).

In the laboratory, natural soils inoculated with *B. dermatitidis* and stored in a refrigerator or a freezer yield the fungus after storage periods as long as 2 months (E. S. McDonough, *personal communication*). Survival of *B. dermatitidis* in natural soils at room temperature is another matter. Studies by McDonough (140, 141, 143) have revealed that 2 weeks after inoculation the fungus cannot be recovered from the soil maintained at room temperature. Control soils sterilized with ethylene oxide and then inoculated with *B. dermatitidis* gave positive cultures as long as 14 weeks after storage at room temperature. Unsterilized soil, when placed directly upon growing colonies of *B. dermatitidis*, produced a marked lysis of the mycelial growth within a 2-week period. Yeast-form cells of *B. dermatitidis* were also lysed by natural soils. McDonough attributed this lysis to a mycolytic agent present in soil. Sterilization of soil by heat or ethylene oxide destroys its lytic activity. It is believed that microorganisms are associated with this phenomenon.

Lysis of fungi in soil has been observed and investigated by a number of workers (13, 43, 87, 130, 160). Bacteria and actinomycetes have been shown to lyse filamentous and unicellular fungi in soil under natural conditions and in vitro. Extracellular enzymes, notably chitinase, lyse living mycelium (103). However, mycolysis is not simply explained by the production of extracellular enzymes by soil microorganisms. Lloyd, Noveroske, and Lockwood (129) believe that autolysis, stimulated by toxic products released by soil microorganisms, may also play a role.

Mycolysis is a highly complex biological activity that merits intensive study. Just what role mycolysis plays in the occurrence and survival of various fungi in soil remains unknown. The discovery that *B. dermatitidis* mycelium and yeast-form cells are rapidly lysed in soil does not preclude the possibility that *B. dermatitidis* exists in a free-living state in nature. Although various phytopathogenic molds are found to be lysed in soil, they survive there and continue to grow, reproduce, and carry on their destructive activities. All available clinical and epidemiological evidence strongly suggests that somewhere in nature an ecological niche exists that favors *B. dermatitidis*. We can be certain that through diligent field and laboratory work its natural habitat will eventually be discovered.

C. immitis RIXFORD AND GILCHRIST, 1896

Geographic Distribution

C. immitis appears to be restricted to the New World. Its endemic areas are situated within specific areas of the United States (Arizona, California, Nevada, New Mexico, Texas, Utah); Mexico (Baja California, Chihuahua, Colima, Coahuila, Durango, Guanajuato, Guerrero, Jalisco, Michoacan, Nayarit, Nuevo Leva, San Luis Potosi, Sinaloa, Tamaulipas, Zacatecas); Guatemala (Montagua River Valley, Zacapa); Honduras (Comayagua Valley); Colombia (Magdalena); Venezuela (Falcon, Lara, Zulia); Bolivia (Santa Cruz); Paraguay (Boquerón, Olimpo); and Argentina (Catamarca, Cordoba, La Pampa, La Rioja, Mendoza, San Luis, Santiago del Estero, Tucuman). That an endemic focus may

exist in Nicaragua is suggested by a canine case of coccidioidomycosis that apparently originated in that Central American republic (159). However, until appropriate epidemiological and ecological studies are carried out, the question as to whether or not *C. immitis* occurs in Nicaragua must remain unanswered.

The several cases of coccidioidomycosis that have been reported from areas outside of the cited endemic areas stemmed either from visits to the endemic areas or from contact with fomites from those areas (15, 84), or they represented misdiagnoses. A series of cases reported as coccidioidomycosis from Ecuador (122), for example, clearly appear to have been cases of paracoccidioidomycosis and leishmaniasis.

Cases of "coccidioidomycosis" originating within the USSR began to be diagnosed in 1951 and continue to the present day (17, 208). However, study of a culture (R-Ko), kindly sent by A. Araviiskii, Pavlov Medical Institute, USSR, showed that the isolate was not *C. immitis*, as determined by its morphology and lack of pathogenicity to guinea pigs. C. W. Emmons (*personal communication*) studied four Russian cultures and concluded that they were haploid forms of basidiomycetes. In recent years, the Russian cases, which have originated in widely separated and different geographic areas of the Soviet Union [Blagoveshchensk (Amurskaya Oblast); Kirghizia SSR, Kiselevsk (Kemerovskaya Oblast); Kuibishev (Kuibreshevskaya Oblast); Leningrad; Moscow (225); Novokuznetsk (Stalinsk) (Kemerovskaya Oblast); Sverdlovsk (Sverdlovskaya Oblast); and Tomsk (111)] are occasionally referred to as coccidioidomycosis-like (116). On the basis of these cultural studies and a critical review of available publications that describe the disease clinically, histologically, and mycologically (18, 116), it appears that the Russian disease does not resemble coccidioidomycosis and that, if the disease is indeed mycotic in nature, an organism other than *C. immitis* is involved.

Prevalence—Human

In the endemic areas of the United States, the incidence and prevalence of *C. immitis* infection is so high that coccidioidomycosis must be considered a major disease. Fiese (84) estimated that about 35,000 new infections occur yearly in California and 5,000 to 10,000 in Arizona. In the most highly endemic areas (San Joaquin Valley, Calif.; Maricopa and Pima Counties, Ariz.; and El Paso County, Tex.), virtually 100% of the inhabitants acquire infection within a few years of residence, and about one-fifth of these develop symptoms severe enough to require medical care.

Data from the mortality reports published by the U.S. Public Health Service show that during the 12-year period, 1952–1963, 733 deaths were attributed to *C. immitis*. The yearly average was 61 (Table 2).

Statistics on the prevalence and incidence of coccidioidomycosis in Latin America either are fragmentary or simply are not available. Skin test surveys carried out in Mexico indicate that *C. immitis* infections are as prevalent there as in the endemic areas of the United States. Glusker (91) found the following percentage of reactors to coccidioidin in Mexico: Baja California, 32%; Sonora, 67%; Chihuahua, 37%; Colima, 33%. In a large-scale and long-term coccidioidin skin test survey, Gonzalez Ochoa (*personal communication*) found the prevalence of reactors also to be high. The prevalence of coccidioidin skin test reactions ranges from 5% to above 50% in the states of Baja California, Chihuahua, Coahuila, Colima, Durango, Guanajuato, Guerrero, Jalisco, Michoacan, Nayarit, Nuevo Leon, San Luis Potosi, Sinaloa, Sonora, and Tamaulipas. Only nine states are considered to be free from *C. immitis*: Campeche, Chiapas, Mexico, Oaxaca, Puebla, Quintana Roo, Tabasco, Veracruz, and Yucatan.

In the Central American endemic areas, skin test surveys have shown that 21% of a group of children in the Motagua River Valley of Guatemala gave positive coccidioidin reactions, and, in the Comayagua Valley of Honduras, skin test surveys by Trejos and Castro revealed an overall prevalence of 25% positivity among the subjects tested (84).

Indications that coccidioidomycosis exists in Colombia are based on publication of two cases (176, 179) and personal observation by Angela Restrepo. Until skin test surveys are carried out in the suspected endemic area in the state of Magdalena and surrounding territory, the size of the zone and severity of the infestation will remain unknown.

The occurrence of coccidioidomycosis in Venezuela is well established on the basis of case reports and skin test surveys. Campins and his co-workers (38) diagnosed the first Venezuelan case in the state of Lara. As a result of their subsequent work and that of others, it is now established that the disease occurs in three states: Falcon, Lara, and Zulia (37).

The other known or suspected endemic areas for coccidioidomycosis in Latin America are found in Argentina, Bolivia, and Paraguay. Historically, Argentina is of the greatest interest because the first known case was reported by Posadas from that country in 1892 (169). Curiously, since that time only 27 additional cases have been diagnosed (Negroni, *personal communication*).

Through the distribution of those few cases and skin test surveys, the endemic areas are considered to be situated, in whole or in part, in the following states: Catamarca, Cordoba, La Pampa, La Rioja, Mendoza, Rio Negro, San Juan, San Luis, Santiago del Estero, and Tucuman. Few coccidioidin skin test surveys have been carried out in Argentina, and thus the magnitude of infections in the endemic areas is unknown. In Santiago del Estero, a skin test survey by Negroni et al. (158) revealed a prevalence of 19% positive reactions among 2,213 children aged 6 to 16 years.

Little is known about the coccidioidomycosis areas of Paraguay and Bolivia. The endemic areas are in the Gran Chaco region that both countries share with Argentina. In Paraguay, Gomez (92) reported that coccidioidomycosis was endemic in the departments of Boquerón and Olimpo. He found that 44% of a group of Guazurangue Indians living in the department of Boquerón gave positive reactions to coccidioidin.

The least studied suspect area is in Bolivia. Our knowledge of the probable existence of the disease there is based on a sketchy report of a single case described by Mackinnon (131) and Artagaveytia-Allende (21). The patient in question had fought in the Gran Chaco during the war between Bolivia and Paraguay. The possibility exists that he may have acquired his infection in Paraguay rather than Bolivia. There is an obvious need for skin test surveys in the Bolivian Chaco to determine whether or not *C. immitis* is in reality endemic in that country's department of Santa Cruz.

Prevalence—Lower Animals

Lower animals are commonly infected by *C. immitis*. In nature, infections have been noted in cats (173), cattle, dogs, coyotes (202), equines, rodents, swine, and in a variety of captive animals: chinchillas, gorillas, llamas, monkeys (84), and a tapir (135).

Studies by Maddy (133) have revealed that cattle infections by *C. immitis* constitute the infectious disease most frequently encountered in California abattoirs. Among the 3,173 cases observed, some had occurred in cattle imported from the endemic areas in Arizona, New Mexico, and Texas. On the basis of skin test surveys, it is estimated that probably several million infected cattle are present in the southwestern United States at any given time (135).

Canine infections are also prevalent in the endemic areas, as shown by clinical cases and skin test surveys (135).

Among wild animals, rodent infections are probably the most numerous. Emmons and Ashburn (77) found infections in several Arizona species of mice and rats: pocket mice, (*Perognathus baileyi, P. intermedius, P. penicillatus*; 15% prevalence in these mice), grasshopper mouse (*Onchomys torridus*), and the kangaroo rat (*Dipodomys meriami*; 17% prevalence in this rat species). According to Maddy (135), Jellison and his co-workers isolated *C. immitis* from two species of rodents collected in the St. George area of Utah, *P. formosus* and *Citellus leucurus* (ground squirrel).

The case of coccidioidomycosis in a rabbit (*Oryctolagus cuniculus*) reported from Hungary by Kemenes in 1954 (108) is considered to represent a diagnostic error. In all likelihood, the infection was due to *Emmonsia crescens* rather than *C. immitis*. The tissue-form cells of *E. crescens*, and also of *E. parva*, are easily confused with the immature spherules of *C. immitis*. A similar error undoubtedly formed the basis for the reports of coccidioidomycosis in two Townsend moles (*Scapanus townsendii*) from the state of Washington (172) and in a cottontail rabbit (*Sylvilagus floridanus*) from North Dakota (210).

The theory proposed by Emmons (68) that coccidioidomycosis is "primarily a rodent disease, transmitted frequently but accidentally to man through the medium of soil contaminated by rodents" was discredited long ago and has been abandoned. There is no evidence substantiating that coccidioidomycosis is transmitted from animals to man or from person to person, or that the presence of *C. immitis* in soil is due to "seeding" by infected animals. All infections are traced to a common source—soil.

Natural Habitat

It is well established that *C. immitis* is a soil-inhabiting organism. From 1932, when Stewart and Meyer (200) first isolated this fungus from soil in the San Joaquin Valley of California, there have been numerous isolations of *C. immitis* from soil samples collected in Arizona (2, 67, 137), California (49, 62–66, 124, 164, 165, 215, 219), and Mexico (194).

The casual report of the recovery of *C. immitis* from Rumanian soil by Evolceanu and Alteras (83) cannot be accepted as authentic. The investigators presented no proof that their two isolates were *C. immitis*. The mere recovery of one of their isolates from an experimentally infected guinea pig after development of a suppurative orchitis does not constitute a valid basis for identification. Many saprophytic organisms survive animal passage and may even stimulate tissue reactions. Development of endosporulating sporangia in an experimental animal is one of the most fundamental and essential criteria for establishing the identity of *C. immitis*.

Our knowledge of the ecology of *C. immitis* is

more advanced than that of other fungi under discussion. It has been unequivocally established that *C. immitis* is a soil-inhabiting fungus superbly adapted to life in semiarid regions. Maddy (137) directly observed the development of *C. immitis* colonies in covered, moistened shallow pits that he had dug in desert areas near Phoenix, Ariz. Mycelial growth, later identified as *C. immitis*, first appeared on pieces of decaying vegetation that were present in the soil. Kaplan and I (*unpublished data*) have directly observed arthrospores of *C. immitis* in Arizona soil samples by staining the supernatant fraction of soil suspensions with fluorescent antibodies.

The Egebergs, Elconin, and Maddy, with their associates, have been instrumental in providing an insight into the ecological requirements of *C. immitis*. Maddy (134) has shown that the conditions that favor the existence of *C. immitis* as a saprophyte in soil occur in those areas that fall into Merriam's (153) biological entity known as the Lower Sonoran Life Zone. In the biotic province, summer temperatures are high, winters are mild, and rainfall is sparse. Maddy summarized the conditions that favor *C. immitis* as follows: "an arid or semiarid climate, alkaline soil, relative freedom from severe frosts, and a very hot, dry season of several months followed by some rain. July mean temperatures from 26°C to about 32°C, January mean temperatures from 4°C to about 12°C, and an annual rainfall of about 5 to 20 inches . . . . ."

One exception may exist in Mexico. On the basis of skin test surveys, the tropical states of Colima and Guerrero have been described as possessing endemic foci of *C. immitis*. Ecological and epidemiological studies are needed to determine the basis for this anomaly.

Shreve and Wiggins (188) define a desert as being "essentially a region of low and unevenly distributed rainfall, low humidity, high air temperatures with great daily and seasonal ranges, very high surface soil temperatures, strong wind, soil with low organic content and high content of mineral salts, violent erosional work by water and wind, sporadic flow of streams, and poor development of normal dendritic drainage." As Maddy stated (136), "Only certain types of plants and animals can survive in this environment. This environment, and only this environment, seems to permit *C. immitis* to exist in nature as a soil organism."

During the hot summer months when summer temperatures 0.5 inch below the surface of the soil reach 60 to 71 C for almost 100 days, *C. immitis*, along with most other microorganisms, is killed, but it survives in the lower depths of the soil, especially in and near rodent burrows (137). Plunkett and Swatek (164) showed that *C. immitis* remains viable at depths of 6 to 8 inches, despite the death of its spores and mycelium at the surface during the hot summer months.

Egeberg and Ely (62) and Elconin, Egeberg, and Lubarsky (65) found that none of 275 soil samples collected in California at the end of the San Joaquin Valley dry season yielded *C. immitis*, in contrast to recovery of the fungus from 31 or 20% of 153 soil specimens collected at the end of the wet season. Also of interest was the finding that among 115 rodent burrow soil samples, 18 (or 16%) were positive, whereas only 13 (or 4.3%) of 313 randomly collected surface or subsurface soils were positive. At the end of the 1956 wet season, 43% (13 of 30) of surface soils yielded cultures of *C. immitis*, as did 41% (18 of 44) of rodent burrow samples.

This work revealed: (i) that *C. immitis* is most apt to be present in soil shortly after a rainy season, (ii) that during such a period *C. immitis* is present in the upper inch of soil or in the lining of rodent burrows, and (iii) that *C. immitis* is only found occasionally during the hot dry season. However, during that season, the fungus survives at depths of 4 to 6 inches (164).

These observations raised several questions in the minds of the investigators. Is the scorching summer heat necessary to the life of *C. immitis*? Does the heat create a relatively sterile layer of soil that only needs moisture to favor the development of fungi living below or adjacent to it? Could heat be an ally of *C. immitis*, producing for a transitory period of time an environment free from antagonists and competitors?

Field studies were carried out by the Egebergs and Elconin (64, 66) to seek answers to these cogent questions. A correlation was found to exist between the presence of *C. immitis* in soil and high concentration of calcium, magnesium, sodium chlorides, and sulfates. It was postulated that the salts encouraged the growth of *C. immitis* by acting either as nutritional stimulants or as inhibitors of microorganisms antagonistic to *C. immitis* (66). Two antagonists were isolated from San Joaquin Valley soils—a strain of *Penicillium janthinellum* and two strains of *Bacillus subtilis*. These microorganisms were grown at different temperatures, 18, 27, and 40 C, in media containing 0 to 8% concentrations of NaCl and $CaCl_2$. *P. janthinellum* did not grow at 40 C with or without the salts; growth of the *B. subtilis* strains was not adversely affected by the high temperature, but it was inhibited by the salts. In contrast, *C. immitis* not only tolerated the 40 C temperature, but its growth was stimulated by the combination of high salt concentration and temperature (64).

What emerges from these ecological studies is a picture of a soil fungus adapted to life in a desert habitat. During long periods of extreme heat and aridity, it survives just below the uninhabitable hot surface of the soil or in rodent burrows. After the rainy seasons, it reinvades the surface area where, in a partially sterilized environment, it sporulates heavily. Then, as the soil dries, the winds pick up the infectious spores and contaminate the air.

Just how far the spores of *C. immitis* are dispersed by air currents is unknown. Maddy (137) feels that they are not carried for more than a few miles beyond a given source point. The isolation of *C. immitis* from air in California (102) and in Phoenix, Ariz. (12), does not cast light on this question. The two Arizona isolations were correlated with a severe windstorm that developed locally a few days before the positive samples were collected. It is known that positive soil sites exist in the vicinity of the collecting area.

C. NEOFORMANS (SANFELICE) VUILLEMIN, 1901

Geographic Distribution

This imperfect yeast, in contrast to the previously described fungi, has a cosmopolitan distribution. Since the description of the first human case from Germany by Busse in 1894 (35), cases of cryptococcosis have been reported from all the major regions of the world (27, 123).

Prevalence—Human

Again, the absence of data on the incidence and prevalence of mycotic infections in general limits any discussion of the public health problem posed by this important mycotic disease. Littman and Zimmerman (126) reported that more than 300 cases had been recorded in the literature by the year 1955. The annual number of deaths attributed to *C. neoformans* within the United States since 1952 has averaged 66 per year; the 12-year total (1952-1963) adds up to 788 fatalities (Table 2).

Utz (211) estimated that 200 to 300 cases of cryptococcal meningitis occur annually in the United States. Littman and Schneierson (127) postulated that 5,000 to 15,000 cases of subclinical or clinical pulmonary cases of cryptococcosis occur in New York City alone.

The absence of a sensitive and specific skin test antigen has prevented surveys designed to determine whether or not a benign self-limited form of cryptococcosis exists. Thus, analogies to coccidioidomycosis and histoplasmosis cannot be drawn. But, in view of the heavy and widespread distribution of *C. neoformans* in the environment, it would not be surprising if a benign form of cryptococcosis did exist. A breakthrough is needed in the preparation of antigens for the study of this disease. Announcement of a successful skin test antigen by Salvin and Smith in 1961 (180) was evidently premature. Evaluation of a similar preparation by Bennett, Hasenclever, and Baum (25) showed that numerous apparently nonspecific reactions occurred in "normal" subjects. They concluded that their studies left "the epidemiologic use of the test as yet undetermined."

Prevalence—Lower Animals

Cases of cryptococcosis have been diagnosed in a surprisingly large variety of animals. The species I cited in a previous review (3) were: cats, cattle, cheetah, civet cat, dogs, ferret, guinea pig, and horses. Subsequently, cases have been reported in a gazelle (178), goats (47, 203), koalas (22, 28, 29), mink (209), and a wallaby (178).

The largest number of infections have occurred among dairy cows suffering from mastitis caused by *C. neoformans*. More than 186 cows have been involved (3, 184).

All evidence indicates that the source of human and lower animal infections is exogenous. Although *C. neoformans* has been isolated from the equine intestinal tract (213), there is no evidence that this fungus is transmitted from animals to other animals or humans, or that animals play a significant role in the dissemination of *C. neoformans* into the environment.

Natural Habitat

Soil is the ultimate source of all infections caused by *C. neoformans*. Sanfelice (181, 182), who was the first to isolate *C. neoformans* from a nonliving source, discovered it while studying the organisms that developed in the juices of various fruits. In retrospect, Sanfelice's isolate is seen as an airborne contaminant that entered the unsterilized containers that he used to hold 200 to 300 ml of fermenting fruit juices. Airborne contamination may also have been the source of the *C. neoformans* strains isolated from "country" milk by Klein in 1901 (109) and by Carter and Young in 1950 (40). Emmons (71) was the first to reveal the presence of *C. neoformans* in soil. Four isolates of that fungus were recovered from 716 soil samples collected in Loudoun County, Va. Subsequent soil studies by Emmons (72, 73) brought to light the significant relationship of *C. neoformans* to pigeons, or, more precisely, to their droppings. Most of the 20 isolates of *C. neoformans* reported upon in 1954 were obtained from sites contaminated by pigeon droppings or, most importantly, from "weathered pigeon drop-

pings." With this clue that *C. neoformans* was probably significantly associated with pigeons, Emmons formed the hypothesis that "pigeon manure may provide a suitable or preferential medium for the saprophytic growth in nature of *Cryptococcus* . . . . ." This hypothesis was put to test by collecting 111 samples of old pigeon nests (essentially composed of excrement) and of pigeon droppings collected under roosting sites, and screening them for the presence of *C. neoformans*. From these 111 samples, 63 (57%) yielded *C. neoformans*. The amazing concentration of *C. neoformans* cells in pigeon manure was reported by Emmons (76) to be in the realm of 50,000,000 viable cells per gram of dry fecal matter.

It remained for Staib to provide a plausible explanation for the pigeon dung-*C. neoformans* association. In a series of studies, he (196, 197) demonstrated that pigeon manure serves as an enrichment medium for *C. neoformans* by virtue of its chemical make-up. Among the constituents of bird urine, uric acid and the purines (guanine and xanthine) are assimilated by the various species of *Cryptococcus*. Creatinine ($C_4H_7N_3O$) proved to be an exception. This compound is assimilated only by *C. neoformans* and not by the other species of that genus. Tests with other yeasts and isolates of *Cryptococcus* showed that members of the genera *Bullera*, *Candida*, *Debaryomyces*, *Lipomyces*, *Pichia*, *Rhodotorula*, *Sporobolomyces*, *Trichosporon*, and *Torulopsis* could not utilize creatinine as a nitrogen source. One isolate of *C. laurentii* proved to be exceptional in that it did assimilate this compound. Thus, we apparently have a biochemical basis to account for the frequent presence of *C. neoformans* in droppings of pigeons and presumably of other birds (195).

This phenomenon of the predilection of *C. neoformans* for avian habitats is well nigh universal. *C. neoformans* has been isolated from bird nests and droppings from: (i) several areas in the United States other than those surveyed by Emmons (100, 101, 107, 127, 155, 171, 204); (ii) Asia (104, 220); (iii) Europe (26, 85, 99, 118, 163, 199, 216); and (iv) Austral-Asia (86).

The striking concentration of *C. neoformans* in bird excrement should not make us overlook the existence of this interesting yeast in habitats clearly unrelated, or not obviously related, to avian habitats. Evenson and Lamb (82) recovered *C. neoformans* from 9 of 20 samples of slime flux exuded by mesquite trees (*Prosopsis juliflora*) growing in the Tucson area of Arizona. That the slime flux of this tree may have a selective property for *C. neoformans* is suggested by the absence of this fungus from exudates of the saguaro (*Cereus giganteus*), cottonwood (*Populus fremontii*), and desert oak (*Quercus oblongifolia*). *C. neoformans* also has been isolated from wood (142) and soil (3, 86, 117, 118, 189). These findings indicate that *C. neoformans* may live in soil free from avian droppings in low numbers, owing to competitive pressure exerted by other soil microorganisms. It is postulated that cells from such areas, carried by wind currents to concentrations of creatinine-rich bird excrement, are deposited in a natural medium favoring their growth and multiplication. Avian habitats thus become the prime source of human and animal infection.

It should be emphasized that the relationship of birds to *C. neoformans* is an indirect one. Natural infections of birds by *C. neoformans* have not been demonstrated. Staib (198) stated that *C. neoformans* is nonpathogenic for canaries and pigeons. The yeast, when fed to canaries, was excreted in a viable state as long as 8 days after the feeding. However, the birds did not become infected. In contrast, Takos (205) found that marmosets (*Leontocebus geoffroyi*) developed systemic cryptococcosis, including brain involvement, when they were fed banana sandwiches with a filler of *C. neoformans*.

It has been suggested that the high body temperature of birds (110) and rabbits (119, 120) is unfavorable for the multiplication of *C. neoformans*.

This hypothesis may not be valid, as was shown by Staib's (198) experiments in which *C. neoformans* cells remained viable in the gut of canary birds as long as 8 days, and by demonstrations that pigeons injected by the intracerebral route developed meningitis and systemic infection (128). What bearing these experiments have on the epidemiology of cryptococcosis is unclear. However, spontaneous *C. neoformans* infections in pigeons and other birds have yet to be demonstrated.

H. CAPSULATUM DARLING, 1906

Geographic Distribution

Histoplasmin skin test surveys and soil studies have definitely established that *H. capsulatum* has a global distribution (4–6, 59–61). Recent reports from the USSR added that country to the list of those where histoplasmosis is endemic (20). On the basis of a critical review of European reports of histoplasmosis and soil studies carried out in Italy, it has been established that *H. capsulatum* occurs in the soil of the Emilia-Romagna region of Italy, and that apparently autochthonous cases of histoplasmosis have been diagnosed in Albania, Austria, France, Great Britain, Hungary, Italy, Portugal, Romania, Switzerland, and

Turkey (192, 193). The vast territory of China is the only major region where valid cases of histoplasmosis have not yet been recorded.

Prevalence—Human

The number of individuals that have been infected by *H. capsulatum* is estimated in the millions. Skin test surveys carried out in the United States, for example, have revealed extensive areas where 30% or more of the inhabitants give positive reactions to histoplasmin: Arkansas, Indiana, Kansas, Kentucky, Mississippi, Missouri, Ohio, Oklahoma, Tennessee, and Texas (61). Similar regions are present throughout Latin America: Brazil, Colombia, Ecuador, French Guiana, Honduras, Mexico, Panama, Surinam, and Venezuela (60).

The fortunate fact that histoplasmosis is basically a benign disease is reflected in the data on annual deaths due to the respiratory mycoses in the United States (Table 2). During the 12-year period (1952–1963), the average death rate due to histoplasmosis was 68, with a grand total for the period of 820.

Prevalence—Lower Animals

A large variety of both feral and domesticated animals have been victims of *H. capsulatum*, as shown in Table 3. Excluded are the reports of Collier and Winckel (44, 45) and Wildervanck et al. (217) on the occurrence of histoplasmosis in a large variety of amphibians, birds, insects, and mammals. The evidence presented in their reports suggests that these investigators were dealing with artifacts rather than with the tissue-form cells of *H. capsulatum*.

Next to man, the dog is the animal most susceptible to infection by *H. capsulatum*. In a review, Menges et al. (151) cited 481 cases in that species. Except for one case each from Brazil, the Panama Canal Zone, and Venezuela, all had occurred in the United States.

Recent studies have shown that bats also fall victim to *H. capsulatum* (Table 3). The fact that *H. capsulatum* has been isolated from their tissues and fecal contents has led to speculation that these flying mammals play an active role in the epidemiology of histoplasmosis. Campbell (36) has suggested that bats might not only be involved in the transmission of *H. capsulatum* from focus to focus but that "the bat *is* the source of the infective agent." She also though it "reasonable to predict that an increase can be expected in the number of microfoci of *H. capsulatum* in nature and—possibly in geographic areas in which the disease has not heretofore been found."

These deductions are considered to be unwarranted. Bats are hapless victims of *H. capsulatum*, as are all other susceptible mammals. There is no evidence that their distribution patterns are changing significantly and that infected bats are creating an ever-growing number of new foci of infection in nature. The geographic distribution of *H. capsulatum* does not appear to be controlled or governed by bats.

Natural Habitat

Emmons first established the fact that *H. capsulatum* lives and develops in soil. In 1949 (69, 70), he recovered the fungus from 2 of 387 soil samples collected in Virginia. Tuberculate macroconidia, characteristic of *H. capsulatum*, were directly noted in saline suspensions of the two positive soil specimens. This significant observation revealed that *H. capsulatum* actively grew and reproduced asexually in soil, since macroconidia are not produced in infected animals. The presence of *H. capsulatum* could not be attributed to contamination of the soil by animals and to the mere survival of the fungus elements so deposited there.

As the result of intensive field studies carried out by Zeidberg and Ajello, and their collaborators, in Franklin County, Tenn., it was discovered that *H. capsulatum* was not haphazardly distributed in soil. The fungus was found to have a significant association with chicken habitats (223, 223). Of 493 soils collected, 28 yielded *H. capsulatum*. Analysis of the source of the positive specimens revealed that 21 (75%) had been collected either inside chicken houses or in chicken yards. Among the other seven positive soils, one had been collected near a dwelling at a site grossly contaminated with chicken manure.

On the basis of these findings, it was concluded that "*H. capsulatum* appears to prefer soils upon which chickens have congregated." It was felt that the association of *H. capsulatum* with chickens was indirect. There was no evidence that chickens developed histoplasmosis and thus could serve as reservoirs for the fungus. Histoplasmin skin tests conducted on chickens in Tennessee (223) and Missouri (144) showed that the prevalence of positive reactors was negligible. Efforts to infect chickens with mycelial suspensions of *H. capsulatum* have ended in failure (149). The experimenters concluded that "chickens were resistant to infection and that the fungus was rapidly destroyed in their tissues." Evidently the normally high temperature of birds (ca. 42 C) prevents the growth of *H. capsulatum* in their bodies. In vitro studies have revealed that inocula of the mycelial form of *H. capsulatum* do not grow at 42 C (146, 224). On the basis of these experimental findings

TABLE 3. *Summary of animal cases of histoplasmosis*

Species	Reference	Species	Reference
CHIROPTERS		CARNIVORES	
Artibeus jamaicensis (fruit bat)	113	*Domestic*	
Carollia perspicillata (short-tailed fruit bat)	114	*Felix domesticus* (cat)	79, 147
Chilonycteris rubiginosa (greater mustached bat)	114, 187	*Canis familiaris* (dog)	79, 151
Desmodus rotundus (South American vampire bat)	56	MARSUPIALS	
Glossophaga soricina (South American long-tongued bat)	114, 138	*Feral*	
Lonchorhina aurita (long-eared bat)	56	*Didelphis marsupialis* (common opossum)	206
Micronycteris megalotis (little big-eared bat)	114, 115	*D. virginiana* (Virginia opossum)	79
Mollosus major (small free-tailed bat)	112, 114	*Marmosa mitis* (mouse opossum)	206
Phyllostomus discolor (long tongued spear-nosed bat)	113	*Philander opossum* (four-eyed opossum)	206
P. hastatus (greater spear-nosed bat)	114	RODENTS	
CARNIVORES		*Feral*	
Feral		*Marmota monax* (woodchuck)	79
Meles meles (badger)	32	*Mus musculus* (house mouse)	79
Mephitis mephitis (striped skunk)	5, 79	*Proechimys semispinosus* (spiny rat)	206
Procyon lotor (raccoon)	5, 148	*Rattus norvegicus* (brown rat)	79, 190
Spilogale putorius (skunk)	78	*R. rattus* (black rat)	78, 183
Urocyon cineroargenteus (grey fox)	5, 79	*Captive*	
Vulpes fulva (red fox)	5	*Chinchilla laniger* (chinchilla)	33
Captive		UNGULATES	
Mustela furo (ferret)	125	*Domestic*	
Ursus middendorfii (big brown bear)	46	*Bos taurus* (cattle)	151
		Equus caballus (horse)	151
		Ovis aries (sheep)	151
		Sus scorfa (swine)	150

and the absence of reports of natural infections in chickens (186), there is no basis to consider chickens as active carriers of histoplasmosis.

Soil surveys and searches for the source of outbreaks of histoplasmosis have revealed that habitats of birds other than chickens harbor *H. capsulatum*. Soil from roosts of grackles (*Quiscalus quiscula*), pigeons (*Columba livia*), and starlings (*Sturnus vulgaris*) have been found to be infested by *H. capsulatum* (41, 75), as well as caves frequented by oil birds (*Steatornis caripensis*) in Peru, Venezuela, and Trinidad (2, 4, 5, 8, 10, 121).

Soils from bat caves and other areas frequented by these mammals, in many different parts of the world, have also yielded *H. capsulatum* (1, 9, 11, 14, 39, 50, 52, 74, 80, 93, 94, 157, 161, 166, 168, 206, 207). It is believed that soil enriched with bat and bird dung gives a competitive advantage to *H. capsulatum* so that it can develop with greater success than it would in another habitat. Extracts of chicken and starling manure have been shown in have a stimulating effect on the sporulation of *H. capsulatum* (95, 191, 212).

The presence or absence of bat and bird dung in the environment does not solely govern the occurrence and distribution of *H. capsulatum* in nature. Other ecological factors also must be at play, for *H. capsulatum* is not invariably present in avian and chiropteran habitats. Throughout the world, there are may areas populated with bats and birds that are free from *H. capsulatum*, as determined by negative soil findings and low or negligible levels of histoplasmin reactivity in the population.

Goodman (95) carried out a series of experiments on a variety of environmental factors that conceivably affected the growth of *H. capsulatum* in nature. He found that in soil with 12% moisture *H. capsulatum* survived temperatures of −18, 4, 10, and 37 C over a 50-week period of observation. In contrast, it did not remain viable longer than 2 weeks when incubated at 40 C. Between 37 and 40 C, there was a dramatic loss of heat tolerance. In dry soil (2% moisture), *H. capsulatum* withstood significantly higher temperatures. At the end of 15 weeks, viable fungal elements were still present in soil cultures maintained at 40 C. But, after 50 weeks, the 37 and 40 C cultures were dead.

The temperature range in which *H. capsulatum* survived was considered to be representative of

that prevailing in the histoplasmosis endemic areas of the United States. Goodman believes that "soil temperatures of 40 C are not likely to occur in the endemic areas, especially not in shaded, moist environments commonly associated with fungal growth." Furthermore, his "data indicate that *H. capsulatum* is not likely to survive in regions where the temperatures rise to 40°C for prolonged periods such as the desert Southwest or Southwestern plains."

Goodman's observations are in contrast to those obtained by Menges et al. (146). In those earlier studies, growth of the fungus was obtained under laboratory conditions only at 100% relative humidity with no growth at 5 or 10 C.

Physical and chemical analyses of soils showed that *H. capsulatum* would not grow at *p*H levels below 5 or above 10. Between those extremes, growth was abundant. Earlier, Zeidberg et al. (223) noted that in Williamson County, Tenn., *H. capsulatum* was recovered primarily from acidic soils.

Goodman found that such chemical factors as nitrogen, phosphorous, potassium, and organic content did not seem to have a significant influence on the growth of *H. capsulatum*. It was not possible to determine on the basis of such analyses why some soils did not support the growth of *H. capsulatum* whereas others of apparently similar composition did.

In 1954, Zeidberg (224) suggested that red-yellow podzolic soils provide the best natural habitat for *H. capsulatum*. This theory was based on the observation that the geographic distribution of histoplasmin sensitivity coincides to a remarkable degree with that of the red-yellow podzolic soils.

More recently, Stotzky (201) proposed another soil theory. This investigator holds that clay minerals are important determinants of the "ecology and population dynamics of microorganisms in soil." Mineralogic analysis of soil samples positive for *H. capsulatum* from widely scattered geographic areas revealed that the soils, with two exceptions, did not contain swelling three-layer silicates (montmorillonite). Stotzky suggested that the distribution of *H. capsulatum* is influenced by the types of clay minerals present in the soil. Although many of the positive soils that he tested were not red-yellow podzolics, he noted that one of the characteristics of red-yellow podzolic soils is the absence of montmorillonite-type clay minerals.

None of the proposed theories satisfactorily accounts for the indisputable association of *H. capsulatum* with bat and bird habitats and its pattern of geographic distribution. The factors involved must be complex, and much work remains to be done to identify them and to understand their inter-related functions.

CONCLUDING REMARKS AND SUMMARY

This survey will have served its purpose if it spurs more investigators to delve into the ecology of human pathogenic fungi. A long, fascinating, arduous, but rewarding road lies ahead for those who take up this study. The relationships of fungi to their environment and to other microorganisms is complex, and much information remains to be gathered before we can begin to understand the host of factors that influence their survival, growth, and distribution in nature.

B. dermatitidis presents one of the greatest ecological challenges. As yet, its natural habitat remains unknown. It is difficult to imagine the precise ecological conditions it requires that permit its existence in such diverse regions as the Americas and Africa. Further studies should be directed not only toward a search for *B. dermatitidis* in as wide a variety of habitats as possible but also toward its possible association with plants and lower animals.

Ecological studies directed toward *C. immitis*, *C. neoformans*, and *H. capsulatum* have been quite fruitful. These three fungi are adapted to life in specific habitats that give them survival and competitive advantages over other microorganisms.

C. immitis is restricted to the desert areas of North, Central, and South America. There, adaptation to high temperatures, low rainfall, and high concentrations of salt enables it to thrive. Outside of the arid regions of the Americas, this fungus evidently cannot establish itself and survive. It would appear that, without drastic climatic changes, the coccidioidomycosis endemic areas will not change appreciably.

Although the absence of *C. immitis* from the arid regions of Africa, Asia, and Australia has not been conclusively established, all available evidence indicates that this fungus does not exist outside of the American deserts. Bates (23) points out that there has been relatively little opportunity for the interchange of desert-adapted plants and animals from one continental desert area to another. This is a consequence of formidable oceanic barriers that separate the great desert regions of the world from one another.

Habitats that favor the growth of *C. neoformans* and *H. capsulatum* occur throughout the world. The oceans do not appear to have barred their spread. But their occurrence in the several continents is not haphazard. Each of these two species is confined to specific habitats that give them survival advantages.

C. neoformans flourishes in bird manures, especially that of pigeons. Staib has shown that this association may be governed by the presence of creatinine, which is utilizable as a nitrogen source by *C. neoformans* but not by competing microorganisms.

It has been established that *H. capsulatum* has a predilection for bat and bird habitats, but the basis for this association has yet to be determined. The role of soil types and climate also bears further investigation.

In the coming decades, ecologically oriented investigations coupled with microbiological and biochemical studies promise to cast new and fresh light on the natural history of the fungi that cause human respiratory diseases.

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