AIRBORNE HISTOPLASMOSIS

MICHAEL L. FURCOLOW

U. S. Public Health Service, Department of Health, Education, and Welfare, Communicable Disease Center, Kansas City Field Station, Kansas City, Kansas

Of all known pathogens, the fungi are by nature perhaps the most ideally suited to cause airborne infection. The common method of propagation among plants involves the production and dissemination of seeds or spores. Characteristic of most fungi is the ability of a single organism eventually to produce thousands of these minute aerial spores. Nature provides a marvelous excess of these tiny particles which, once mature, are rapidly dispersed by the slightest air currents. In this airborne state they are subject to the extremes of environment before a small fraction of their original numbers, by chance, finds a suitable site for germination. However, although only a few spores may germinate and continue the species, each of the myriads originally produced is endowed (by virtue of a hard capsule) with a remarkable capacity to survive. Most fungal spores are capable of withstanding relatively extreme variations in temperature and humidity and can remain viable for long periods of time even in the dried state. For some, even direct sunlight for brief periods is not lethal. These are the characteristics of the fungi which are of most importance to us: their capacity to produce innumerable infectious particles, the minute weight and size of the spore particles which allows them to become truly airborne, and the remarkable capacity of each particle to survive extremes in the environment and remain potentially infectious.

It is apparent, therefore, that airborne infection in man and animals is only an accidental occurrence in the life cycle of the fungi. Indeed, it is usually an unfortunate accident for the fungus since the organism itself is at a dead-end. However, once the vegetative spore of a pathogenic fungus enters the host, still another remarkable capacity becomes evident. This is the capacity to germinate not into the mold but into a completely different tissue or yeast phase. This adaptation takes full advantage of the new environment which provides optimal temperature and metabolic fuel for the new form which is now a true parasite.

The varied forms and intricate reproductive cycles of many fungi have been described for decades, but interest and scientific inquiry into the mechanisms and importance of the airborne mycotic infections have been undertaken only recently. My purpose is to summarize the existing data relating to one of the most fascinating of these organisms, *Histoplasma capsulatum.*

Knowledge of histoplasmosis as a fungal disease of both man and animals has had a rapid development following the lead of Dr. C. E. Smith in using the skin test as an epidemiological tool. By this means histoplasmosis has been transferred from classification as a rare and fatal disease to recognition as a common, relatively benign one since 1945. Because of its tendency to infect river valleys rather than desert areas and the propensity of people to inhabit these same areas, estimates have been made that 30,000,000 people are infected in the United States (13). This appears not to be an unrealistic figure and may be rather low, as Emmons and others report new areas of endemicity outside of what we formerly considered the high endemic area. In short, it is probable that all the major river valleys of the United States are infected to varying degrees. Increasing evidence indicates similar involvement of the three major river valleys of South America and much of Africa. Burma, India, Thailand, and Indonesia are also endemic areas. It appears from present evidence that probably all the major river valleys of the world between latitudes 45°N and 45°S are infected. Although much of the information is fragmentary and is a combination of skin-test data and case reports, the knowledge obtained from studies in the United States supports these seemingly wild estimates.

Much of the knowledge of histoplasmosis has come from studies of airborne epidemics. Drs. Dingle, Langmuir, and Smith were involved in studying one of the first of these at Camp Gruber, Oklahoma. Epidemics have continued to give us keys to the story of histoplasmosis as will be illustrated by the report of the recent

acquisition of knowledge regarding urban histoplasmosis.

It has been known for some time that urban individuals were infected from at least two sources (1, 5), namely, visits to a farm or prior residence on a farm or by exposure in urban structures contaminated by bird droppings. Kier et al. (10) reported exposure to contaminated soil brought into cities from farms for use as fertilizer as a third source.

The fourth source recently found was exposure in wooded open areas in the city contaminated by bird droppings. This source of infection is illustrated by an epidemic which occurred in Mexico, Mo., a town of about 15,000. In April 1959, four boys developed chills, fever, and cough. Roentgenographic examination, serological studies, and skin tests confirmed the original impression of histoplasmosis. Their only association was in Boy Scout activities, and all had onset of illness 12 to 14 days after a group of some 64 boys cleaned an 11-acre plot which was to become a city park. The boys raked leaves, burned them, and in general had a good frolic.

The plot with its ante-bellum house had been purchased by the city because of its historical value. Originally a show place, the grounds had been unkept during the past 20 years and although during this period the city grew around the plot, the site itself became a wilderness of overgrown trees, shrubs, and debris. Subsequent inquiry revealed that since 1950, for at least 5 years, large numbers of starlings, from 10,000 to 100,000 birds, had nested on this property. The disturbance and stench created by these birds bothered the entire neighborhood, so that around 1955 control measures were instituted which resulted in the disappearance of the birds from the area, although evidence of bird droppings was still found on the ground at the time of the epidemic.

As seen from Table 1, it was quite evident that the boys who worked on the property had probably all been infected and that the site of the epidemic unquestionably was the park. These conclusions were further supported by data of Table 2, which show the isolations of *H. capsulatum* from soil collections at the site. It is seen that 62% of the soils collected from this property were positive for *H. capsulatum*. The sites of soil collections on the property and the areas of Boy Scout activity are shown in Fig. 1.

TABLE 1. *Histoplasmin skin test, serology, and roentgenographic findings in the Mexico, Mo., histoplasmosis epidemic*

	Worked in park	Did not work in park
Skin Test:		
Total tested	64	46
No. positive	62	19
% Positive	97	41
Serology:		
Total tested	60	32
No. positive	36	8
% Positive	60	25
X Ray:		
Total tested	60	36
No. positive	28	9
% Positive	47	25

TABLE 2. *Recovery of Histoplasma capsulatum from soil collections from Historical Society Park, Mexico, Mo.*

Date collected	No. of samples collected	No. positive by culture	Per cent positive
5-6-59	6	5	83
7-14-59	26	15	58
9-16-59	26	16	62
Total	58	36	62

An investigation was made to determine whether the incidence of positive cultures from this park was unusual and a total of 68 soils was collected from shaded areas near creek beds in the neighborhood of Mexico, Mo., as illustrated in Fig. 2. Only 1 of these 68 soils was positive for *H. capsulatum*. These findings indicated an important new source of urban infection with *H. capsulatum*.

Re-investigation of other urban epidemics unrelated to previously known sources made clear their relationships to gregarious bird harborage. For instance, the 1948 epidemic associated with digging for fishing worms in an area of Madison, Wis., has been related to blackbirds and starlings by a recent investigation (2). Secondly, an epidemic in Walworth, Wis. (14), where 19 persons were infected at the site of digging in a cellar, was also related to starlings having roosted in the area. According to H. A. Dickie, H. Bayley, and R. F. Poser (*unpublished studies*, 1956), a third

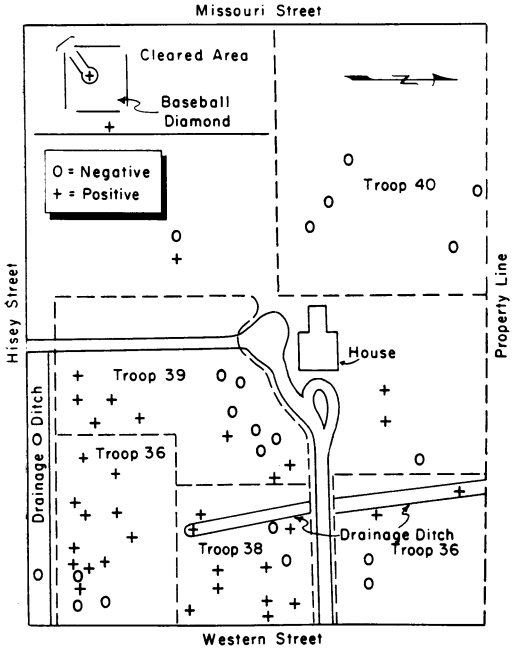

FIG. 1. *Sites of soil samples tested for Histoplasma capsulatum in Historical Society Park, Mexico, Mo.*

epidemic in Columbus, Wis., was related to pigeon droppings contaminating the shrubbery about a church where 23 persons were infected.

Two urban endemic areas now appear to be epidemiologically related to the starling. Among school children in Dalton, Ga. (3), the histoplasmin sensitivity rate was 60% in the city and 20% in the surrounding country. Infection apparently occurred in the wealthier parts of town, and it was found on investigation that these parts of town were shaded areas where thousands of starlings had roosted.

In Milan, Mich., another endemic area has been reported where the sensitivity rate in the city is over 60%, compared to 2 to 11% in the surrounding country (4). Here, starlings were present in such abundance that city sidewalks were white with droppings.

It is quite clear, therefore, that urban histoplasmosis is an important entity and that its spread in urban populations is related very closely to soil enrichment by bird droppings, particularly where there are significant aggregations of urban birds such as starlings.

The recent development of knowledge of cavitary histoplasmosis resembling tuberculosis has presented a new and important aspect of this problem. Studies based on more than 32,000 sera of patients in tuberculosis sanatoriums indicate the presence of positive *Histoplasma* serological tests in about 7% of patients. When the percentages found in the various areas of histoplasmin sensitivity are applied to the sanatorium populations in these areas, it can be estimated that there are between 7,000 and 8,000 cases of histoplasmosis resident or recently resident in tuberculosis sanatoriums in the United States (Table 3) (6). Some of these have tuberculosis as well. Since histoplasmosis patients are not benefited by antituberculous therapy, the importance of this problem is obvious.

The clinical manifestations of histoplasmosis vary from the mildest sort of influenza-like illness to acute, disseminated disease resembling septicemia or typhoid. Symptoms in the chronic type of disease resemble those of tuberculosis, namely, production of sputum, weight loss, and slow progression without therapy, with a tendency to occur more frequently in older age groups. The tools for investigation of clinical cases are the skin test, serological studies, culture, and histopathological examinations.

The skin test gives some cross reactions with both blastomycin and coccidioidin. However, the specific skin tests, in our experience, are usually more strongly positive than the cross reactions. The same applies to the serological tests, of which there are a variety. However, the most useful appears to be the precipitin test, either done by the tube or agar diffusion method, and the complement-fixation tests employing histoplasmin and yeast-phase antigens.

Culture appears to be difficult for a variety of reasons, among which are the rather slow growth rates of the pathogenic fungi, differing characteristics with different incubation temperatures, and the overgrowth of cultures with airborne saprophytes.

Histopathological recognition appears to be improving continually with the development of newer and better stains. At present the methenamine silver stain seems to be the most useful in demonstrating the presence of fungal elements in the tissues.

Critical Analysis

One of the important tools of investigation, serological investigation, is not readily available

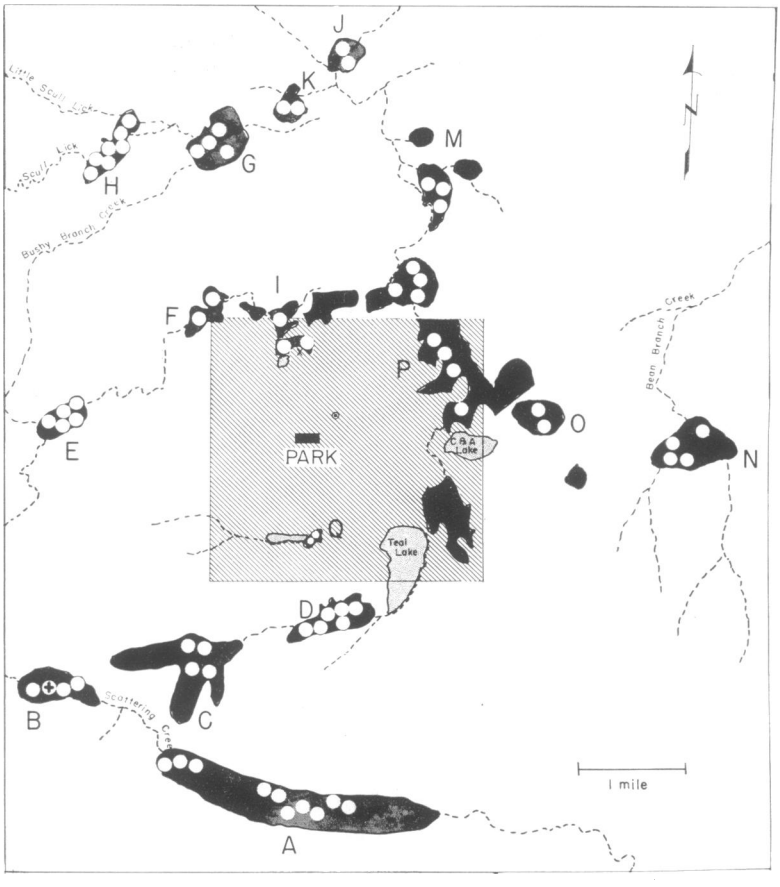

FIG. 2. *Sites tested for Histoplasma capsulatum in the vicinity of Mexico, Mo.*

in many parts of this country. This lack has hampered the clinician in the development of knowledge of the disease. A further difficulty is the relatively slow development of skin test and serological reactivity. This means that patients with acute histoplasmosis are rarely diagnosed. Since physicians tend to lose interest in the diagnosis after the patient has improved clinically, retesting is seldom done at the time when serological and skin test evidence is clear-cut. Knowledge of the cultural peculiarities of fungi in the laboratory is not widespread, and many laboratories appear to have missed the organism due to their lack of knowledge of the specific characteristics of the fungi in culture or failure to handle the cultures properly. The histopathological tool, methenamine silver stain, appears to be used in relatively few laboratories. It is clear, therefore, that maximal advantage is not taken of the tools which are presently available.

Further difficulties in the studies of the organism develop when one moves into the experimental laboratory. Studies of airborne infection with *H. capsulatum* must concern themselves with spore size. As is evident in Fig. 3, there is an abundance of small *Histoplasma* spores (70 to 95% less than 4.8 μ in size) which are ideal for intrapulmonary retention.

Table 4 compares infection of mice exposed on naturally and artifically infected soil. It is seen that 86% of the mice were infected by 1 day's exposure on naturally infected soil, and all of the mice were infected by 1 day's exposure on artificially infected soil. In other words, the organism readily enters the lungs of mice exposed on either artificially or naturally infected soil.

In Fig. 4 it is seen that the intranasal inoculation of even small numbers of spores, as few as 10, results in a steady increase in mortality with the passage of time. Indeed, it appears that 10

TABLE 3. *Estimated number of tuberculosis hospital admissions* due to histoplasmosis by areas of histoplasmin sensitivity*

Histoplasmin sensitivity in area	No. of admissions to federal and nonfederal TB hospitals (1959)	Per cent positive by serology on survey	Estimated no. of histoplasmosis patients
%			
>80	11,100	9.4	1,043
30–80	21,000	8.3	1,743
10–30	39,800	5.5	2,189
<10	69,200	4.1	2,837
Total.....	141,100		7,812

* Data from Hospital Statistics (9).

TABLE 4. *Exposure of mice for 1, 2, and 4 days to soils seeded with Histoplasma capsulatum*

Infected soil	No. days exposed	No. mice positive/ no. autopsied	Per cent positive	Per cent tissue positive		
				Liver	Spleen	Lung
Natural	1	6/7	86	86	86	86
	2	7/7	100	100	100	86*
	4	6/7	86	86	86	86
Artificial	1	7/7	100	100	100	100
	2	7/7	100	100	100	100
	4	7/7	100	100	100	100
Controls	—†	0/7	0	0	0	0

* Plates containing lung tissue from one mouse were contaminated.

† Not exposed.

Data from Hinton, Larsh, and Stilberg (8).

spores are almost as effective as a lethal inoculum as 10,000 to 100,000 spores.

Although it is thus clear that *H. capsulatum* can infect intranasally with relatively small numbers of spores, all is not as simple as it first appears to be. For instance, included in this measured "spore" inoculum were both macroconidia and microconidia as well as viable nonbranching mycelial fragments not included in the spore count. At the time we could not arrive at a microscopic count which correlated with a viability count unless we counted all the fragments. Reference to Table 5 shows that apparently all the elements of *H. capsulatum* have viability, either

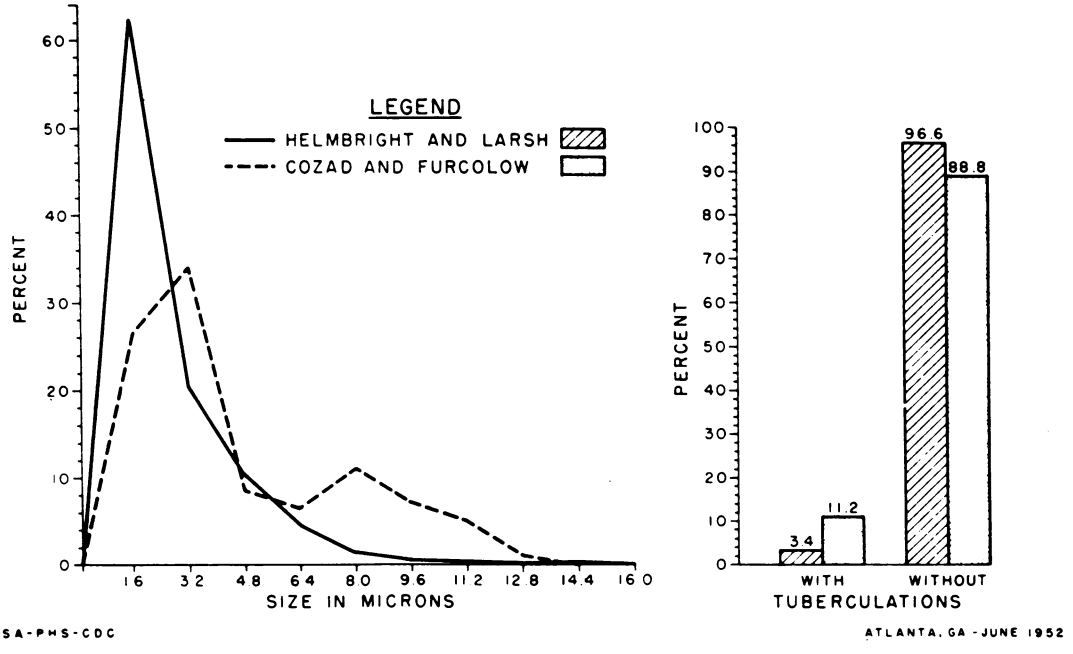

FIG. 3. *Comparison of the size and presence of tuberculations of the spores of the same 5 strains of Histoplasma capsulatum by two observers. Helmbright measurements made on strains approximately 6 months old; Cozad on strains approximately 5 months old. All cultures from potato dextrose agar slants. (From Helmright and Larsh (7a).)*

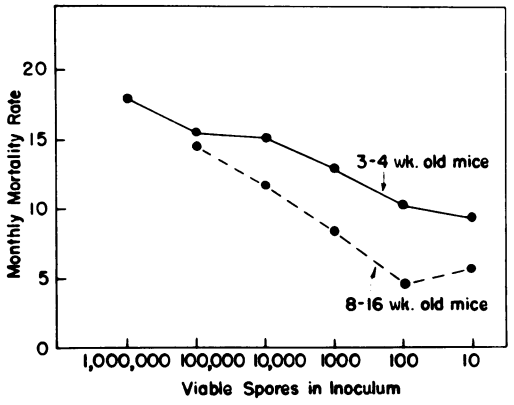

FIG. 4. *Mice infected intranasally with Histoplasma spores. Effect of age of infected mice on mortality. (Adapted from Grayston et al. (7).)*

in the white mouse or chick embryo, or both. Therefore, one cannot afford to disregard in the microscopic counts any of the mycelial fragments present. It should be emphasized that these latter studies were performed with single-particle elements.

The mortality of mice infected with *H. capsulatum* by either the intranasal or intraperitoneal route is quite comparable as shown in Table 6. Although the inoculum in Table 6 is described as "viable spores," this is subject to the sizable error due to mycelial particles mentioned above. Repeated studies have demonstrated a low order of viability for both spores and mycelia. As was indicated in Table 5 and confirmed in further studies, the viability of mycelial particles from various isolates ranged from less than 1% to a high of 19%. A mycelial particle in these experiments was defined as any particle visible in the microscope, following a harvest of the culture from Sabouraud's medium by shaking with glass beads. This harvest therefore included both mycelial elements and spores. In other words, the highest viability in a large number of observations was only 19% of all the visible elements. Studies of the viability are further complicated because of the influence of the medium which is used, much higher counts being obtained on medium containing blood than on plain Sabouraud's medium. Thus, the problem is complicated not only by the differing viabilities of the three types of particles (large spores, small spores, and mycelia) but also by the variations in results obtained by plating identical particles on different media. Other variables include age of the culture at harvest and the varying growth rates and viabilities of different isolates. These variations assume major proportions in airborne experiments, especially if one is attempting to immunize animals or determine the effect of immunization.

TABLE 5. *Percentage of white mice and chick embryos infected by single-particle inoculum of 3-month-old culture of the Ellis isolate of Histoplasma capsulatum*

Units inoculated	White mouse		Chick embryo	
	Infective ratio*	Per cent infected	Infective ratio	Per cent infected
Nongerminated tuberculated macroconidia	4/48	8/2	0/40	0.0
Nongerminated microconidia	1/47	2.1	3/42	7.1
Germinated tuberculated macroconidia	3/48	6.2	7/51	13.7
Germinated microconidia	1/19	5.3	3/51	5.9
Nonbranching mycelial fragments	0/20	0.0	4/28	14.3
Total	9/182	5.0	17/212	8.0

* Number of animals infected/number of animals inoculated.

Data from Larsh et al. (12).

TABLE 6. *Effect of route of inoculation on uncorrected mortality of 3–4-week-old mice infected with spores of Histoplasma capsulatum*

Viable spores in inoculum	Route of inoculation					
	Intranasal			Intraperitoneal		
	Total	Deaths		Total	Deaths	
		No.	Per cent		No.	Per cent
1,000,000	106	19	17.9	—	—	—
100,000	923	144	15.6	278	36	12.9
10,000	544	82	15.1	29	8	27.6
1,000	1,106	144	13.0	307	33	10.7
100	502	51	10.2	115	7	6.1
10	880	81	9.2	115	11	9.6
Total....	4,061	521	12.8	844	95	11.3

Data from Grayston, Altman, and Cozad (7).

TABLE 7. *Sensitization of guinea pigs by two exposures to Henderson aerosol and by subcutaneous injections, using formalin-killed yeast and mycelial-phase cells of Histoplasma capsulatum*

Inoculum	Route of inoculation	No. guinea pigs per group	No. guinea pigs positive to 1:10 histoplasmin	Per cent positive	No. weeks required to sensitize*
Mycelial particles	Aerosol†	14	14	100	7 to 10
	Subcutaneous	10	10	100	5 to 12
Whole yeast cells	Aerosol‡	10	8	80	7 to 11
	Subcutaneous	10	10	100	7 to 10
None (control)		14	0	0	

* Experiment terminated after 20 weeks.
† Five-hundred particles/g pig initial dose, 1,000/g pig after 6 weeks.
‡ Nineteen-hundred cells/g pig initial dose, 3,800/g pig after 6 weeks.
Data from Larsh (11).

Similar difficulties do not arise when the inoculum is composed of whole yeast cells, whose viability is very high. Table 7 indicates that formalin-killed particles, either mycelial or yeast, by either aerosol or subcutaneous methods, are capable of inducing histoplasmin sensitivity in nonsensitive guinea pigs. It is evident, therefore, that skin sensitivity, at least, can be induced in guinea pigs with nonviable material.

The production of immunity, however, is an entirely different question. It is, in fact, difficult, if not impossible, to give a dose of living *H. capsulatum* organisms in the mycelial phase without giving, at the same time, a tremendous inoculation of nonliving organisms.

Table 8 shows, however, that a calculated dose of only three viable mycelial particles could produce skin test sensitivity. Furthermore, the conversions occurred somewhat more rapidly than those occurring after exposure to nonviable particles alone. Until we are able to produce suspensions of mycelial particles with high percentage viability, that portion of the sensitivity or immune response which is actually due to viable material will have to be measured by comparisons of the effects of vaccines of mixed viability and totally nonviable materials.

TABLE 8. *Histoplasmin sensitivity in guinea pigs as a result of exposure to aerosols of viable mycelial and yeast cells of Histoplasma capsulatum*

Inoculum	No. viable cells per guinea pig	No. guinea pigs per group	No. guinea pigs positive to 1:10 histoplasmin	Per cent positive	No. weeks required to sensitize
Mycelial particles...	3	13	11	84.6	1–6*
Whole yeast cells....	76	11	10	90.9	3–4†
None (control).....	0	13	0	0	—

* Experiment terminated after 14 weeks.
† Experiment terminated after 16 weeks.
Data from Larsh (11).

S. Saslaw, S. B. Salvin, S. Marcus, and others have reported similar immunization experiments. I have focused on our own experience to illustrate the many inherent difficulties in this type of approach.

Significance to Public Health and Defense

With half a million infections and a thousand deaths a year in the United States, the importance of *H. capsulatum* to public health is self-evident. The problem is at least three-fold:

1) Acute illness: Although it appears that only one-third to one-half of the individuals receiving a minimal infection are ill enough to complain, the infection may be fatal in susceptible individuals, especially the young. Symptoms accompanying infection appear more severe in adults than children. The illness accompanying large doses of the infectious agent is regular and severe. In the Camp Gruber epidemic over 80% of exposed persons became ill, with an average hospitalization period of over 6 months, and 18 of 25 were finally given disability discharges.

Many patients complain of malaise and debility for months after infection.

2) Complications of healing: Histoplasmoma, chronic atelectasis, bronchiectasis, and mediastinal fibrosis occur with healing of the acute infection. The character of the fibrosis in mediastinitis makes operative correction almost impossible. Surgical resections of histoplasmomas because of suspicion of cancer result in hundreds of dangerous operations yearly, many unnecessary.

3) Relapses or endogenous reinfections: Occurring mostly in later life, relapses are mounting public health problems. Present estimates of over 7,000 active cases in tuberculosis sanatoriums and steadily increasing rates of positive serological tests observed in sanatoriums continuously support the increasing importance of the problem. In the four sanatoriums for which all admissions over a 3-year period have had a serological test for histoplasmosis, the rates of reaction have doubled (from 6 to 12%). These estimates do not include the many patients with this disease who are refused admission or otherwise sidetracked before being hospitalized because their sputa are negative for tuberculosis. Preliminary estimates indicate at least a thousand new cases a year.

The serious nature of histoplasmosis is indicated by follow-up of 100 untreated cases. With average follow-up of less than 4 years, one-third are dead and two-thirds of those surviving are at least 50% incapacitated. There is every reason to believe the frequency of recognition will increase as cavitary tuberculosis decreases. The pressing nature of the problem of care is indicated by the decrease in tuberculosis hospital personnel at the very time there is a rising rate of histoplasmosis.

Biological Warfare Implications

The natural occurrence of all infections with *H. capsulatum* by the airborne route should lead to its serious consideration as a biological warfare agent. The stability of the spores for years without special media, temperature controls, or need of specialized personnel in handling, and their probable resistance to explosive damage, point to their usefulness. The illness engendered by the spores, especially if given in a sizable dose, would affect all exposed persons and last for several weeks. Recovery of most would be probable. In addition, presently available knowledge indicates that world-wide climatic conditions would enable infection to be temporary or permanent in any area. Thus, in an arid area use of *H. capsulatum* would be preferable, unless permanent infection were desired, whereas in a more humid area, *Coccidioides immitis* would be preferred.

The fungi seem to be ideal biological warfare agents in many ways, such as ease of handling, ease of dissemination, resistance to damage by explosives, production of severe but temporary illness in most cases, ability to cause temporary or permanent infection of local areas depending on the organism selected, selection of immune troops for duty in infected areas by history of residence or actual skin test, and possibility of actively immunizing all troops.

Acknowledgments

Appreciation is expressed for the cooperation of Howard W. Larsh, J. Thomas Grayston, and George C. Cozad in these studies and to Alexander D. Langmuir and Harold J. Lynch, Jr., for assistance in the writing of the manuscript.

Literature Cited

1. Anderson, N. W., I. L. Doto, and M. L. Furcolow. 1958. Clinical, x-ray and serologic changes with *Histoplasma* infection. Public Health Repts. **73**:73–82.
2. Dickie, H. A., H. Ackerman, and M. Murphy. 1953. *In* M. L. Furcolow and J. T. Grayston, Occurrence of histoplasmosis in epidemics, etiologic studies. (Summary). Am. Rev. Tuberc. **68**:307–320.
3. Edwards, P. Q., L. Ajello, J. Moore, C. F. Jacobs, and D. L. Aronson. 1960. Soil sampling in an urban focus of histoplasmin sensitivity. Am. Rev. Respirat. Diseases **81**:747–751.
4. Engelke, O. K., S. M. Hemphill, E. Bushell, and E. B. McKinney. 1960. A survey of tuberculin and histoplasmin reactors among school children of Washtenaw County, Michigan. Am. J. Public Health **50**:368–376.
5. Furcolow, M. L., and P. Ney. 1957. Epidemiologic aspects of histoplasmosis. Am. J. Hyg. **65**:264–270.
6. Furcolow, M. L., J. H. Schubert, and F. E. Tosh. 1960. High incidence of histoplasmosis in sanatoriums in the United States. N. T. A. Meeting May 15–19, 1960, Los Angeles, Calif. Am. Rev. Respirat. Diseases. (*to be published*).

7. GRAYSTON, J. T., P. L. ALTMAN, AND G. C. COZAD. 1956. Experimental histoplasmosis in mice, a preliminary report. U. S. Public Health Monograph No. **39**:99–105.

7*a*. HELMRIGHT, A. L., AND H. W. LARSH. 1956. The size of the spores of *Histoplasma capsulatum*. U. S. Public Health Monograph No. **39**:81–83.

8. HINTON, A., H. W. LARSH, AND S. L. SILBERG. 1957. Direct exposure of mice to soils known to contain *Histoplasma capsulatum*. Proc. Soc. Exptl. Biol. Med. **94**:176–179.

9. Hospital Statistics. 1960. Hospitals **34**:359–404.

10. KIER, J. H., C. C. CAMPBELL, L. AJELLO, AND W. D. SUTLIFF. 1954. Acute bronchopenumonic histoplasmosis following exposure to infected garden soil. J. A. M. A. **155**:1230–1232.

11. LARSH, H. W. 1960. Natural and experimental epidemiology of histoplasmosis. Ann. N. Y. Acad. Sci. **89**:78–90.

12. LARSH, H. W., V. E. SCHOLES, A. HINTON, AND S. SILBERG. 1958. Minimal infection inoculum of *Histoplasma capsulatum* for mouse and chick embryo. Proc. Soc. Exptl. Biol. Med. **98**:570–573.

13. LOOSLI, C. G. 1955. Histoplasmosis—some clinical, epidemiological, and laboratory aspects. Med. Clin. N. Am. **39**:171–199.

14. WILCOX, K. R., JR., B. A. WAISBREN, AND J. MARTIN. 1958. The Walworth, Wisconsin, epidemic of histoplasmosis. Ann. Internal Med. **49**:388–418.