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# GEOGRAPHICAL DISTRIBUTION OF HISTOPLASMOSIS AND HISTOPLASMIN SENSITIVITY

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Histoplasmosis was first described clinically by Darling in 1906,[91] diagnosed as a mycotic infection by Da Rocha Lima in 1912,[87] and the causative agent, *Histoplasma capsulatum*, was cultivated and described by De Monbreun in 1934.[97] For many years the disease was regarded as an acute, rare, and fatal illness in man characterized in typical cases by extensive, generalized involvement of the reticulo-endothelial system with fever, lymphadenopathy, hepato-splenomegaly, pulmonary infiltration, leukopenia, anaemia, and, not infrequently, ulcerations of the oral or intestinal mucosa. In January 1945, Parsons & Zarafonetis published a clinical review of the 71 cases which had been reported in the medical literature, 56 from the USA and the remaining 15 from all over the world ; all but four of these cases were fatal.[256]

Also in 1945 evidence was first presented that, surprisingly contrary to accepted belief, fatal cases were the exception rather than the rule—the infection appeared to be widespread, in certain areas, in a benign and asymptomatic form, rarely recognized clinically. The first indication for this unexpected development was in the observation by a number of different investigators that, in certain areas of the USA, high proportions of persons with pulmonary calcifications did not react to tuberculin. This observation was generally interpreted as evidence that tuberculin sensitivity disappears after complete healing of the lesion, as calcification was thought to result only from specific infection with the tubercle bacillus. Yet it was impossible to reconcile this explanation with the fact that there were marked geographical variations in the percentage of tuberculin-negative persons who had calcifications.

Meanwhile, workers in the south-western part of the USA—the area where coccidioidomycosis is endemic—had shown that the pulmonary form of that fungus disease frequently heals by calcification and, consequently,

that many coccidioidin-positive, tuberculin-negative persons had pulmonary calcifications. In 1943, Smith, who for many years had been interested in fungus diseases, pointed out that the geographical area where the highest frequency of calcifications was observed in tuberculin-negative persons coincided with the area in which histoplasmosis, a fungus disease in some respects closely related to coccidioidomycosis, was known to occur.[326] Subsequent combined x-ray and skin-testing surveys—using various fungus antigens, including histoplasmin—led to the publication in 1945 of two reports, one by Christie & Peterson [65] and the other by Palmer,[248] which clearly demonstrated a high correlation between pulmonary calcifications and histoplasmin sensitivity in tuberculin-negative persons. A subsequent, detailed report by Palmer, on the geographical distribution of histoplasmin sensitivity among groups of student nurses throughout the country, showed that the highest frequency of histoplasmin reactors was found in the east-central part of the USA [249]—the area in which clinical cases of histoplasmosis have been repeatedly observed.

Although based primarily on epidemiological and statistical considerations, these observations constituted strong evidence that, in addition to tuberculosis and coccidioidomycosis, histoplasmosis also produces, and in certain areas is the principal cause of, pulmonary calcifications. Furthermore, in 1949, Furcolow was able to show, by serial x-rays over a period of two to three years, the development of calcifications from benign, asymptomatic, pulmonary infiltrations, otherwise indistinguishable from tuberculosis, in a group of tuberculin-negative, histoplasmin-positive persons.[120] *H. capsulatum* was successfully recovered from two of these cases.

A great many cases of histoplasmosis, varying in severity from asymptomatic infiltrates to acute, massive, pulmonary involvement or localized cutaneous or mucosal ulcerations, have been diagnosed clinically, and by culture of the organism in some cases, within the past few years, particularly in the upper Mississippi Valley region in the USA. Cases are also being found in Argentina and Brazil, and single, isolated cases have been reported from several other countries. From the available case reports, clinical histoplasmosis appears to occur in persons of all ages, more frequently in males than females and, perhaps, more frequently in the white races.

Nothing is known of how the infection takes place. A man-to-man infection has never been demonstrated, and, although the fungus and the disease have been observed in many animals (dogs, cats, horses, ferrets, rats, skunks), there is no verified case of transmission from an animal to a human being. Emmons' recent success in isolating the fungus from soil is an important contribution to the problem of how the disease is transmitted.[110]

Since infection with *H. capsulatum* has been found to result in sensitivity to histoplasmin, skin-testing has become an important tool in the epidemiological study of histoplasmosis. From extensive reports of testing

experience with various antigens, it appears that strong reactors to histoplasmin may also react to some extent to other immunologically related antigens just as weak reactions to histoplasmin are at times observed in individuals infected with other fungi. Cross-reactions with tuberculin have not been observed in sufficient frequency to create a problem. However, there is little doubt that, in an area where histoplasmosis is known to be present, a definite reaction to histoplasmin is generally construed as evidence of infection with *H. capsulatum.*

During the past six years in which the story of histoplasmosis has been gradually unfolding, the medical profession throughout the world has shown an increasing interest in determining the prevalence and distribution of this infection. The purpose of this paper is to bring together available information from many sources in order to draw a picture of the worldwide distribution of histoplasmosis and histoplasmin sensitivity—a picture which must, necessarily, be viewed as preliminary and incomplete at this time. An effort was made to obtain and review the case reports and studies of histoplasmin sensitivity which have appeared in the literature before January 1951. In addition, findings are given of a number of hitherto unpublished studies, many of which were carried out by independent investigators, in various parts of the world, to whom histoplasmin was supplied by the Tuberculosis Division of the US Public Health Service (see table II, page 265). Results of studies supported by, or conducted in co-operation with, the WHO Tuberculosis Research Office, Copenhagen, are also included, and constitute a substantial contribution to the worldwide picture of histoplasmin sensitivity as it appears today. Recognition of areas where sensitivity has been reported provides an indication of where histoplasmosis may occur, and the relatively small number of cases diagnosed outside the USA and Canada offers additional leads for further studies of the epidemiology of histoplasmosis.

## Reported Cases of Histoplasmosis

### *North America*

Most of the 146 cases diagnosed in the USA are in a well-defined area in the east-central part of the country. The greatest number of cases has been observed in Missouri, fewer in the adjacent States. Although increased awareness of histoplasmosis in certain States probably leads to more frequent diagnoses, there is little doubt that the disease is more prevalent in the territory roughly limited by the Arkansas and Mississippi rivers to the west, the Great Lakes to the north, the Appalachians to the east, and the Gulf of Mexico to the south.

Generalization concerning the actual frequency of clinical histoplasmosis is difficult, because in certain areas the diagnosis is now made so often that case reports are no longer published. For example, it is pointed out in

one paper that of a total of 17 cases diagnosed at the Vanderbilt University Hospital, Nashville, Tennessee, up to 1948, only 6 have been published.[178] In another paper, a review of 2,135 surgical cases of appendicitis during a ten-year period at the Henry Ford Hospital, Detroit, Michigan, states that organisms identified as *H. capsulatum* on microscopic examination were reported in 103 of the pathological specimens—5% of the cases—confirming the view that the infection is much more prevalent than is indicated by the number of clinical cases described in the literature.[271]

Histoplasmosis has never been reported in Alaska, and only two cases have been observed in Canada.[140]

All cases outside the USA and Canada reported in the literature from 1906 to 1951, which have been diagnosed by demonstration of the fungus either by microscopy or culture, are listed according to geographical origin in table I and are briefly reviewed in this section.

In spite of the fact that the first three cases of histoplasmosis were found by Darling in Panama, no additional cases have been diagnosed there since 1907.[92] Two of his three cases occurred in young negroes from Martinique, one of them having been in Panama only three months before death.

Two cases have been diagnosed in Mexico,[259, 361] and one in Honduras.[261] The latter, however, has been considered doubtful by some authors.[19] Histoplasmosis has never been found in the West Indies.

*South America*

The number of cases diagnosed in South America is second only to that in the USA. In Brazil, where nine cases of *Histoplasma* infection have been observed, five were discovered during a survey in 1939-45 in connexion with yellow-fever studies of approximately 170,000 liver-biopsy specimens, mainly of children.[251, 349] One case has been reported from Colombia [129] and two from Uruguay.[9, 53] Several observations have been published in Argentina since Negroni succeeded in isolating and cultivating the fungus.[234]

*Australia, New Zealand, and the Pacific*

One case of histoplasmosis was reported in Honolulu, Hawaii, in 1947 [197] and one from the continent of Australia in 1948.[177] Histological specimens of a localized skin-growth of a farmer, a lifetime resident of the Orange district, New South Wales, were positive for *H. capsulatum*, but cultures were not made.

*Asia*

Histoplasmosis has apparently never been diagnosed on the continent of Asia or in Japan.

Three cases of *H. capsulatum* infection have been observed in Java, although none has been reported from other Indonesian islands. In 1932, histoplasmosis was found in eastern Java at the autopsy of a seven-year-old native boy, a resident of Toendjoengredjo, Lomedjang district.[233] A fatal

**TABLE I. DATA FOR 46 CASES OF HISTOPLASMOSIS DIAGNOSED MICROSCOPICALLY OR BY CULTURE, 1906-51, ACCORDING TO GEOGRAPHICAL SOURCE OF REPORT ***

| Country | Report | | Sex | Age (years) | Race or nationality | Diagnosis | Remarks |
|---|---|---|---|---|---|---|---|
| | ref. no. | date | | | | | |
| Anglo-Egyptian Sudan | 176 | 1949 | M | 35 | Sudanese | biopsy | Resident of Wad Medani, Blue Nile province |
| Argentina | 234 | 1938 | M | 40 | White | biopsy | Resident of the State of Buenos Aires |
| Argentina | 21 | 1941 | M | 33 | White | autopsy, culture | Resident of the State of Buenos Aires |
| Argentina | 20 | 1943 | M | 49 | White | biopsy | Resident of the Federal District |
| Argentina | 238 | 1946 | M | 53 | White | biopsy, culture | 15 years resident of Buenos Aires |
| Argentina | 118 | 1947 | M | 43 | White | biopsy | 8 years resident of Argentina |
| Argentina | 262 | 1949 | M | 52 | White | biopsy | 51 years resident of Argentina |
| Argentina | 241 | 1950 | M | 50 | White | biopsy | Yugoslav, 21 years resident of Buenos Aires |
| Australia | 177 | 1948 | M | 51 | White | biopsy | Lifetime resident of New South Wales |
| Austria | 269 | 1925 | M | — | White | autopsy | — |
| Brazil | 6 | 1939 | M | — | — | biopsy, culture | — |
| Brazil | 7 | 1941 | — | — | — | sputum culture | Tuberculosis diagnosed clinically |
| Brazil | 349 | 1941 | M | 3 | Mulatto | autopsy | Resident of Recreio, Minas Gerais |
| Brazil | 54 | 1943 | M | 60 | Negro | — | — |
| Brazil | 105 | 1945 | F | 23 | Negro | autopsy | Resident of Andaral, Bahia |
| Brazil | 251 | 1946 | M | 2 | Negro | autopsy | Resident of Xiririca,, São Paulo |
| Brazil | 251 | 1946 | F | 6 | Negro | autopsy | Resident of Itapé, Bahia |
| Brazil | 251 | 1946 | F | 3 | White | autopsy | Resident of Itapé, Bahia |
| Brazil | 251 | 1946 | F | 9 | Mulatto | autopsy | Resident of Pernambuco |
| Bulgaria | 257 | 1950 | M | 4 | White | biopsy, culture | — |
| Colombia | 129 | 1947 | F | 56 | White | autopsy | Born in Venezuela |
| England | 101 | 1942 | M | 30 | White | autopsy, culture | Several years resident of India and Sudan |
| French Sudan | 62 | 1945 | M | 26 | Negro | biopsy, culture | Resident of Bamako village |
| French Sudan | 186 | 1947 | F | 15 | Negro | autopsy, culture | Resident of Sikasso village |
| Hawaii | 197 | 1947 | M | 45 | White | autopsy | Resident of Hawaii |
| Honduras | 261 | 1926 | M | 24 | Honduran | autopsy | — |
| Java | 233 | 1932 | M | 7 | Javanese | autopsy | Resident of Toendjoengredjo, East Java |
| Java | 37 | 1949 | M | 43 | Chinese | autopsy, culture | Lifetime resident of Java |
| Java | 151 | 1949 | M | 35 | Chinese | biopsy | 20 years resident of Java |
| Mexico | 259 | 1943 | M | 68 | White | biopsy, culture | Many years resident of Mexico |
| Mexico | 361 | 1945 | — | — | — | — | — |
| Netherlands | 312 | 1937 | M | 63 | White | autopsy | Resident of Dutch East Indies |
| Panama | 91 | 1906 | M | 27 | Negro | autopsy | From Martinique |
| Panama | 92 | 1907 | M | 29 | Negro | autopsy | From Martinique |
| Panama | 92 | 1907 | M | 55 | Chinese | autopsy | 15 years resident of Panama |
| Philippines | — [a] | 1926 | M | 40 | Filipino | autopsy | — |
| Portugal | 359 | 1943 | F | 59 | White | autopsy | Lifetime resident of Portugal |
| Spain | 58 | 1945 | F | 44 | White | culture | Lifetime resident of Spain |
| Turkey | 256 | 1946 | M | 38 | White | autopsy | Resident of Istanbul |
| Turkey | — [b] | 1949 | M | 24 | White | biopsy | Resident of Ankara |
| Union of South Africa | — [c] | — | M | 58 | White | autopsy | Thought to be tuberculosis ante mortem |
| Union of South Africa | 323 | 1942 | M | 55 | White | autopsy, culture | Resident of Rhodesia |
| Union of South Africa | 207 | 1949 | — | — | — | culture | Acute fulminating case |
| Union of South Africa | 207 | 1949 | — | — | — | culture | Acute fulminating case |
| Uruguay | 9 | 1944 | M | 59 | White | biopsy, culture | Travelled in Argentina and Brazil |
| Uruguay | 53 | 1947 | M | 58 | White | biopsy, culture | 17 years resident of Montevideo |

* Cases diagnosed in Canada and the USA are not included.
[a] W. W. Wade—report to the Culion Medical Society, Philippines
[b] K. Mutlu—communication to the Tenth International Medical Congress, Ankara
[c] B. A. Dormer—personal communication

case of the disease, verified by culture, in a forty-three-year-old, Java born, Chinese driver has recently been published, and an unpublished case from the same region, diagnosed histologically, is also mentioned.[37] The latter case may be the same as that reported more recently—a thirty-two-year-old Chinese, resident of Batavia for the last twenty years, in whose case a biopsy specimen was positive.[151]

As early as 1926 a case in the Philippines was diagnosed at the autopsy of a Filipino who also had leprosy and tuberculosis (W. W. Wade—report to the Culion Medical Society, Philippines). Not all authors have agreed with this diagnosis, however.

*Africa*

The first case from the Union of South Africa was recognized in 1942 by histological and cultural demonstration of the fungus.[323] In 1949, two fulminating cases were reported in that region,[207] and an additional unpublished case has been diagnosed in Durban, Natal (B. A. Dormer—personal communication).

French authors have reported two instances of mycotic infections diagnosed as histoplasmosis in indigenous residents of the French Sudan, French West Africa.[62, 186] In both cases the fungus was cultivated successfully, and animal inoculations were attempted.[61] It was reported that the organism in vivo was considerably larger than usually found in America—5-15 $\mu$ in size compared with 3-5 $\mu$.

An interesting case from the Anglo-Egyptian Sudan was described in 1949.[176] A native machine-attendant, working in a cotton-mill in Wad Medani, Blue Nile Province, although suffering from a generalized dissemination, recovered without treatment. Fungi were detected in a biopsy specimen.

*Europe*

Histoplasmosis has been reported only occasionally in Europe, and it is not unlikely that some of these cases may have been imported. The disease was diagnosed in England, for example, in a soldier who had been garrisoned for several years in India and the Sudan.[101] Another case was reported in a man who had lived for many years in the Dutch East Indies before retiring to the Netherlands.[312]

Single cases have been noted in Portugal [359] and Spain,[58] both in middle-aged women who had never been outside their respective countries.

From Vienna, Austria, postmortem findings were described in 1925 of a patient who had been suffering from recurrent, severe exanthema over the entire body for more than six years.[289] Numerous intracellular organisms were observed in the tissue sections at autopsy, and, although blastomycotic infection was suspected, subsequent authors have suggested that *H. capsulatum* infection is a more likely diagnosis.

The case of a four-year-old child in Bulgaria with multiple bone-lesions demonstrated by x-ray examination was published in 1950.[257] Cultures from histological sections of external femoral tissue revealed double-contoured extra- and intra-cellular oval organisms believed to be *H. capsulatum*.

One case was reported in 1946 from Istanbul, Turkey,[296] and another in 1949 from Ankara (K. Mutlu—communication to the Tenth International Medical Congress, Ankara, Turkey), each diagnosed by microscopy. In addition, it is of interest to note that a cat with *Histoplasma* infection was recently found in Ankara.[3]

## Histoplasmin Sensitivity

In contrast to the relatively small number of cases of histoplasmosis—about 200 by the end of 1950—histoplasmin sensitivity has been reported in a substantial number of countries. Any attempt to draw a picture of the worldwide distribution of sensitivity must be recognized as very preliminary, because of the great variations, among the reported studies of histoplasmin sensitivity, in the potency of different histoplasmin preparations,[a] the technical procedures followed, interpretation of reactions, and selection of localities and persons for testing. The sources of the products used in histoplasmin-sensitivity studies are given in table II. Several large-scale

**TABLE II. SOURCES OF PRODUCTS USED IN HISTOPLASMIN-SENSITIVITY STUDIES**

| Source | Dilution | Number of studies |
|---|---|---|
| US Public Health Service—National Institutes of Health | | |
| Emmons, H-3 | 1/1,000, 1/100 | 3 |
| US Public Health Service—Tuberculosis Division | | |
| Howell, H-15 | 1/1,000, 1/100, 1/200 | 12 |
| Howell, H-40 | 1/1,000, 2/1,000 | 20 |
| Howell, H-42 | 1/100 | 4 |
| Lach | 1/1,000 | 1 |
| Lilly | 1/1,000, 1/100 | 9 |
| Negroni | 1/10 | 1 |
| Oliveira Lima | 1/1,000, 1/100 | 1 |
| Peterson | 1/100 | 1 |
| Not specified | 1/1,000, 1/100 | 18 |
| Total | | 70 |

[a] The source, lot number, and dilution of antigen used in each study, if reported, is given in parentheses throughout the text.

surveys in the USA, however, conducted with uniform technique, provide comparable data for mapping histoplasmin sensitivity throughout the nation.[249] A rather general and incomplete mapping of sensitivity elsewhere in the world is shown in fig. 1, indicating areas where relatively high, moderate, and low levels of sensitivity to histoplasmin have been reported, areas where histoplasmin-testing has yielded negative results, and areas where no studies have been made.

Perhaps the most striking impression given by this map is that the highest prevalence of histoplasmin sensitivity is found in the east-central part of the USA, in southern Mexico, Central America, and certain parts of South America. An isolated, low sensitivity area has been reported from South Africa, and almost no histoplasmin sensitivity has been found in Europe, with the possible exception of Italy. Since practically nothing is known of the position in Asia and the Orient, this section of the world is omitted from fig. 1.

*North and Central America*

An intensive effort is being made to establish a more detailed nation-wide picture of histoplasmin sensitivity throughout the USA. Most of the American studies since 1946, when Palmer first reported striking variations in the prevalence of histoplasmin sensitivity among groups of student nurses in different parts of the country,[249] have confirmed his findings that

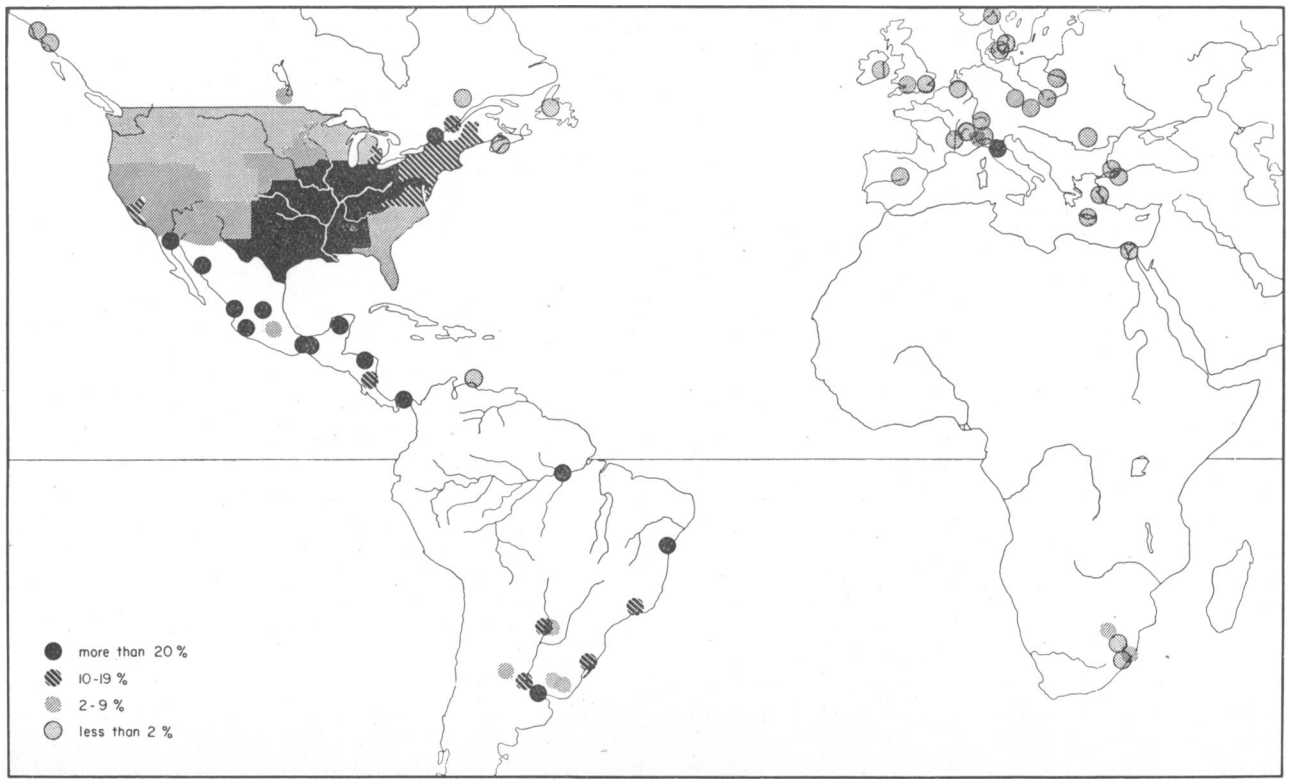
" an area of high prevalence of positive histoplasmin reactors exists in the eastern central part of the United States and that the frequency of positive reactors, in general, decreases with increasing distance from this area."

These findings have been corroborated by several investigators, as well as by a recent study based on tests of many thousands of young adults from all over the country carried out by the Field Research Branch of the Tuberculosis Division of the US Public Health Service (C. E. Palmer—unpublished material). Since the extensive literature from the USA largely confirms and amplifies Palmer's work, a comprehensive bibliography is included in the present paper in place of a detailed review of the material.

Histoplasmin sensitivity in Canada has been found only in the south-eastern provinces. Among 75 schoolchildren from Beloeil, a small town 30 miles (48 km) from Montreal, Quebec, positive reactions to histoplasmin (H-15, 1/1,000), some of which were reported to be very strong, were seen in 20 cases (26.7%).[144] Similar tests of 161 Indians of varying ages in the northernmost part of Quebec—Abitibi-East County—gave quite different results : 8 were positive to both histoplasmin and purified protein derivative (PPD) tuberculin, 96 reacted to tuberculin only, and none to histoplasmin alone.[143] This study revealed a decrease in sensitivity with increasing distance from the area of high prevalence similar to that found in the USA.

Among 270 tuberculosis patients tested twice in 1950 at the Royal Edward Laurentian Hospital, Ste. Agathe des Monts, Quebec, 10.4% were

**FIG. 1. GEOGRAPHICAL DISTRIBUTION OF HISTOPLASMIN SENSITIVITY THROUGHOUT THE WORLD**




Each study is indicated by a circle shaded to represent the percentage of positive reactors reported ; " less than 2% " includes completely negative findings; areas from which no studies have been reported are unshaded (including the continents of Asia and Australia, which are not shown). Nationwide mapping of sensitivity is indicated for the USA.

considered positive histoplasmin reactors (F. L. Phelps—personal communication). Most of these patients were from the Montreal area, although some had travelled extensively.

A group of 440 patients and employees was tested with histoplasmin (Lilly, 1/100) at the Deer Lodge Veterans Hospital in Winnipeg, Manitoba.[140] Positive reactions occurred in 23 individuals, 5 of whom had never been outside Canada. A similar low frequency was reported from Minnesota, USA, which lies immediately south of Manitoba.[249]

At Dalhousie University in Halifax, Nova Scotia, 310 students were tested with histoplasmin (H-15, 1/1,000); 306 were reported negative and only 4 positive, all the latter having been part-time residents of areas outside the Maritime Provinces of Canada.[330] A group of 157 lifetime residents of Newfoundland tested with the same antigen showed no reactions.

No sensitivity to histoplasmin has been found in Alaska, although an interesting study in the Pribilof Islands, Bering Sea, was recently made to determine the specificity of histoplasmin and coccidioidin.[319] Three hundred and fifty-six inhabitants of the Islands, 200 miles (320 km) from the Alaska mainland, were skin-tested with histoplasmin (H-3, 1/1,000), coccidioidin, and tuberculin. The Aleuts had never left the Islands except for a few months in 1943 when they were moved to an army camp just south of Juneau, Alaska, where they were completely segregated with no access to the mainland. Although strong reactions to tuberculin were found, all the persons tested were negative to both the fungus antigens with the exception of one individual who was sensitive to histoplasmin. The subjects were retested with 1/100 dilutions of the two fungus antigens; there were no reactions except in the one person already cited.

Among 140 Alaska Indians, between 15 and 20 years of age, and several hundred children in the villages of Sitka, Wrangell, and Metlakatla, no positive reactions were found with histoplasmin (H-15, 1/100) (J. D. Aronson —personal communication).

South of the USA, high levels of histoplasmin sensitivity have been reported from certain areas in Mexico, Central America, and South America. In the village of Abalá, in the State of Yucatán, Mexico, more than half of a group of 150 persons was reported as positive to histoplasmin, none to coccidioidin.[137] Tests were performed with a 1/100 dilution of antigen obtained from cultures of two different *Histoplasma* strains. An unpublished study quoted in the report mentions a frequency of 18.6% reactors among 1,500 patients in the Mexico City General Hospital, and also quotes results of studies among Indians which showed 32.6% positive in Amantenango del Valle, Chiapas, and as many as 46.4% in San André Chamula, Chiapas.

Sensitivity to coccidioidin, brucellin, haplosporangin, tuberculin, and histoplasmin (Peterson, 1/100) was studied in over 7,000 Mexican Army recruits, 5,000 of whom had lived all their lives in their home States.[132]

While the percentage positive for Mexico City recruits was as low as 3.4, the highest frequency of sensitivity—43%—was found among recruits from the State of Chiapas, with slightly lower sensitivity in persons from the States of Nayarit, Sonora, San Luis Potosí, and Colima. The frequency of positives appeared to be highest among recruits from the south-eastern coast.

Studies in Mexicali, Lower California, of 2,148 persons resulted in 24.2% positive to histoplasmin, with a larger number of reactors among females than males.[325] With coccidioidin, there were 24.6% positive reactors among 2,789 tested. In a group of 162 persons tested with tuberculin (Pirquet method), histoplasmin, and coccidioidin, 13 were positive to histoplasmin only, 9 to coccidioidin only, and 45 to tuberculin only; 48 were positive to all three antigens.

The Tuberculosis Report for 1949 of the Ministry of Public Health of Nicaragua, states that of 137 children (age not specified) tested with histoplasmin (Lilly, 1/1,000), 16% had reactions classified as positive.[240] In some instances, pulmonary calcifications were found in histoplasmin-positive children who were non-reactors to tuberculin, a finding highly suggestive of *H. capsulatum* infection in Nicaragua.

In a study conducted in the Hospital La Lima, Honduras, 300 male patients ranging in age from 7 to 82 years were tested with histoplasmin (Lilly, lot CT-189, 1/100) and coccidioidin (Kessel, 1/100).[160] Both antigens were kept refrigerated during the two weeks before use; new syringes and needles were employed for the tests to avoid contamination by other antigens. Reactions were read 44-48 hours later, and an induration of 5 mm or more was considered positive. One hundred and twenty-five of the patients (41.7%) were reactors to histoplasmin, among whom 13 reacted to both antigens, and 1 patient reacted to coccidioidin only. In a country where histoplasmosis has been diagnosed only once, in 1926, demonstration of such a high frequency of reactors in a careful and well-planned study indicates the need for further investigations to determine the source of sensitivity to histoplasmin.

The correlation between histoplasmin sensitivity and pulmonary calcifications in Curaçao, Netherlands Antilles, was investigated; no reactions classified as definitely positive to histoplasmin were observed among more than 100 persons tested.[260]

A very careful study of general-hospital patients in Cristobal, Panama, showed that 190 of 500 patients reacted to histoplasmin after 48 hours with indurations of 5 mm or more.[344] Two preparations of histoplasmin (Lilly, lot CT-189, 1/100 and H-42, 1/100) were used with new syringes and needles. One hundred and forty-two of the reactors were also positive to 0.0005 mg of PPD. The investigator feels that there is an obvious discrepancy between finding 38% reactors to histoplasmin and the fact that there has been no recognized case of human histoplasmosis in Panama

since 1907. Further studies are being made to determine whether cross-reactions with antigenically related fungi or actual infection by *H. capsulatum*, or both, may be responsible for such a high degree of histoplasmin sensitivity.

*South America*

In Rio de Janeiro, Brazil, 202 patients were tested with histoplasmin (Lach, 1/1,000) in an antituberculosis dispensary; 26.2% reacted with an induration of 5 mm or more.[55] Among the positive reactors, 18 were permanent residents of the Federal District and 27 were from various parts of the country; residence information could not be obtained for the others. Subsequently, the same investigator reported tests among 1,372 patients of the Rio de Janeiro Tuberculosis Dispensary, 145 of whom were positive to histoplasmin (Lilly, 1/1,000 or 1/100).[56]

A study of 108 persons in Salvador, Bahia, revealed 25.2% positive reactors,[56] while in a group of 870 male prisoners of Pôrto Alegre, Rio Grande do Sul, 14.6% reactors to histoplasmin (1/100) were found.[215] The frequency of reactors appeared to be highest in men from the northwestern part of Rio Grande do Sul.

In Santarém, Pará, 187 of 623 schoolchildren (30%) reacted to histoplasmin (H-40, 1/1,000) with 5-mm or more induration (M. A. Morehead & G. Macedo—personal communication). Only 21 of them also reacted to tuberculin. Twenty-one of 66 hospital workers showed definite histoplasmin reactions, and 13 had doubtful reactions (erythema with no induration).

Among 763 persons tested with histoplasmin in Bahia and Rio de Janeiro late in 1949 and early in 1950, a substantial number of reactors (5-mm or more induration) to 1/100 dilution was reported, very few to 1/1,000.[348] Two histoplasmin preparations were used (Oliveira Lima, lot A, 5/2/1949, 1/100 and 1/1,000 or H-40, 2/1,000).

From neighbouring Uruguay approximately 5% of 100 persons tested with histoplasmin had positive reactions.[53] In a subsequent, detailed study of histoplasmosis, the investigator reports that among almost 1,200 persons (hospital and maternity-ward patients and personnel) he observed a positive response to histoplasmin (Lilly, 1/1,000) in 8.9%.[54] Positive reactions were more frequent in men (14.6%) than women (3.3%).

A low degree of sensitivity was observed in Argentina among dispensary patients in the city of Córdoba and tuberculosis patients in the sanatorium of Villa Tortosa (Sierras de Córdoba) near Buenos Aires (G. Sayago & I. F. Wolaj—personal communication). A single injection containing a mixture of three fungus antigens—histoplasmin (H-40, 1/1,000), coccidioidin, and blastomycin—was followed by separate doses of each of the three antigens in persons reacting with more than 5-mm induration. Of 144 dispensary patients, 13 reacted to the mixed injection, and of 11 who returned for separate tests, 8 reacted to histoplasmin only. Of

58 tuberculous patients, 10 were positive to the three antigens together, 7 reacted to histoplasmin alone, and none to the two other antigens.

A somewhat higher percentage of reactors was found in general medical patients in a Buenos Aires clinic,[138] including one confirmed case of histoplasmosis previously described in detail.[118] The histoplasmin was produced by Negroni from an Argentinian strain of the fungus, grown on a modified tuberculin synthetic medium and used in a 1/10 dilution. Of 437 persons tested, 106 (24.3%) had a positive reaction to this antigen; the patient diagnosed as having histoplasmosis did not respond to the test. The majority of allergic individuals came from an area which includes roughly the northern section of the State of Buenos Aires and the State of Santa Fé. The author indicates, however, that his material is too limited to establish a pattern of sensitivity for Argentina.

In Asunción, Paraguay, approximately 2,000 healthy individuals of both sexes and all ages, applicants for health cards, were tested with histoplasmin (H-3, 1/1,000), but because of the small number of reactions observed the dose was increased to 1/100 dilution.[131] About 18% of those tested had indurations of more than 5 mm in diameter, 13% had smaller reactions, and the remainder was negative. A group of 106 patients with progressive, sputum-positive tuberculosis was also tested; there were positive reactions in 2% of the cases. From these studies the investigator feels that histoplasmin sensitivity is not high in Paraguay and that, furthermore, the skin-test is of little value in the differential diagnosis of pulmonary lesions and calcifications because of the very high rate of tuberculinization in the country. Study of the geographical distribution of positive reactors was not attempted.

Results of studies being conducted at the present time in Ecuador with histoplasmin (H-42, 1/100) are not available for inclusion here.

*Asia*

A very limited number of studies of histoplasmin sensitivity has been reported from Asia and the Orient. A series of careful studies in India was recently completed in Darjeeling, West Bengal, and Kelur, south-west of Madras (WHO Tuberculosis Research Office—unpublished material). Tests with histoplasmin and several other antigens, including tuberculin (0.0002 mg of PPD), were given to groups of workers and their families in tea-plantations in the Darjeeling area. A group of 1,159 Indians, between 1 and 20 years of age in approximately equal numbers of both sexes, was tested with histoplasmin (H-40, 2/1,000). Reactions of less than 5-mm induration were observed three days later in all but 9 persons, and in 6 of the 9 histoplasmin reactors the reaction to tuberculin was between 0 mm and 2 mm. No reactions larger than 5 mm were found among 341 schoolchildren in Kelur or among 261 leprosy patients of all ages in the leprosarium at Vada Thorasalur near Kelur.

In Hong Kong, China, 25 adults from 21 to 51 years of age were tested with histoplasmin (H-15, 1/1,000), coccidioidin, and tuberculin in March 1949 (J. R. McMillan—personal communication). Twenty-one Chinese and four Portuguese, all native residents of Hong Kong and Macao, had no reactions to either fungus antigen, although all but one person reacted to tuberculin.

*Africa*

Several reports from the Union of South Africa indicate a low prevalence of histoplasmin sensitivity in that area, although very little is known of the rest of the African continent. A preliminary report was recently published giving results of a study among 140 white persons in the Transvaal, Union of South Africa.[207] The antigens used in that survey were histoplasmin (H-15, 1/1,000), with both coccidioidin (1/100) and saline solution for control tests. In 48 hours, reactions to histoplasmin with an induration of 5 mm or more were found in 11 cases (8%), doubtful reactions (induration less than 5 mm or erythema only) in 6 cases, and no reactions to either coccidioidin or saline solution. Of the 17 positive and doubtful reactors, 8 had lived in the Transvaal all their lives but had taken short vacations in other provinces, 4 had lived previously in the Cape Province, 2 in Zululand, and 1 each in the Orange Free State, Natal, and Southern Rhodesia.

On the Drakensberg, near Durban, Natal, 893 Bantus were tested with histoplasmin (H-15, 1/1,000) (communication from Unit in Tuberculosis, Council for Scientific and Industrial Research, Durban). No positive reactions were reported. When testing 693 Bantus on the coast, however, the investigators found 11 reactors, none of whom showed calcifications in his chest film. Workers in a factory in Durban were tested with the same antigen; among 1,336 persons, 79 (5.9%) were reactors (including 12 tested with 1/200 dilution), among whom 12 were European, 15 Indian, and 52 native.

In the northern part of the African continent, in Mehalla, Egypt, a factory town in the Nile Delta midway between Cairo and Alexandria, 380 adult workers were tested with histoplasmin (H-40, 2/1,000) and tuberculin (0.0002 mg of PPD) (WHO Tuberculosis Research Office—unpublished material). Although there were many tuberculin reactions, no reaction to histoplasmin of 5-mm or more induration was observed in 72 hours.

*Europe*

Except for two reports from Italy, the studies conducted in most of the European countries disclose evidence of virtually no sensitivity to histoplasmin. In the Eastern Mediterranean, a survey of histoplasmin sensitivity was carried out by International Tuberculosis Campaign teams in Crete in the autumn of 1948 (WHO Tuberculosis Research Office—unpublished material). A selection of sample groups with due regard to geographical

coverage was made according to specifications from the WHO Tuberculosis Research Office. Histoplasmin- (H-40, 1/1,000) and tuberculin-tests were given to children living in urban, semi-rural, and rural areas in five different localities. Eight hundred and fifty-nine schoolchildren were tested : 823 were negative, 2 had definite reactions to histoplasmin, and 34 had indurations measuring between 1 mm and 4 mm in diameter. The results of this careful study definitely indicate that the population of Crete is non-allergic to histoplasmin.

In Turkey, three different studies have shown negative results. Early in 1951, inmates of the Istanbul prison were tested with both histoplasmin (H-42, 1/100) and tuberculin (Old Tuberculin, 1/1,000) by one of the authors. Among 348 completed tests, largely in adult males, no reactions to histoplasmin larger than 2-mm induration were present in 72 hours, although a high proportion of the subjects reacted to the Mantoux tests. Chest films taken during the testing period were unsatisfactory because of technical difficulties in developing the film.

No positive reactions occurred in 154 clinic patients tested with histoplasmin (H-15, 1/1,000) in Istanbul,[297] nor were any reactors found in a number of children with pulmonary calcifications in a paediatric hospital in Ankara, although 8 of these youngsters were also negative to tuberculin (S. Ulus—personal communication).

Several studies have been conducted in Italy. Among 50 tuberculous sanatorium patients tested with histoplasmin (Lilly) in central Italy, 12 positive reactors were reported.[338] Two of these 12 patients had been for long periods residents of Libya and Poland, respectively. Studies of 303 subjects with the same type of histoplasmin in northern Italy revealed only 4% positive reactions,[24] and in a study of 183 tuberculosis patients in a Pavia sanatorium, also in the north, only 1 positive and 3 doubtful reactions were observed.[294]

The first of several studies of histoplasmin sensitivity in Switzerland was reported in 1948.[191] One hundred and eighty adult patients of the Clinique médicale de l'Université de Zurich, who had demonstrable calcifications in the lungs or hili, were given 0.1 ml of freshly prepared dilution of histoplasmin (1/100). Only 2 reactors were found, 1 of whom had lived for more than 7 years in the mid-western part of the USA, the other for 25 years on the island of Java. A survey of 555 recruits of the Swiss Army Medical Corps, twenty-year-old men from all parts of the country, rural as well as urban, constituted a small but representative sample of the Swiss population from a geographical point of view. None of the recruits reacted to histoplasmin.

The incidence of sensitivity to histoplasmin and tuberculin in relation to pulmonary calcifications among 1,526 students at the Université de Genève has been carefully studied (E. Grasset & P. Press—personal communication, to authors, of report to the First International Congress of

Allergists, Zürich). Each student had a chest x-ray as well as tests with both histoplasmin (H-40, 2/1,000) and tuberculin (0.0001 mg of PPD). Reactions to both tests were read after 48-72 hours; x-rays were read for pulmonary calcifications without knowledge of the subjects' skin sensitivity to the two antigens.

The first group examined in May-June 1950 was composed of 466 students of various nationalities; nearly half of them were Swiss. A total of 11 persons reacted to histoplasmin, 7 of whom were from the USA, 2 from Canada, 1 from Israel, and 1 from Mexico. Pulmonary calcifications were found in 6 of these histoplasmin reactors, 4 of whom were negative to tuberculin.

A second group of 1,060 students was similarly studied during March 1951. Twenty-four were found to react to histoplasmin with indurations measuring at least 7 mm : 19 were from the USA, 1 each from Canada, India, South America, and Turkey, and 1 Swiss who had lived for nine years in South America. Pulmonary calcifications, sought only among the histoplasmin reactors, were demonstrated in 7 of the 24.

These important investigations clearly demonstrate that no histoplasmin sensitivity exists in Switzerland. Furthermore, the findings illustrate how a study of pulmonary calcification in association with histoplasmin and tuberculin sensitivity may be used to determine whether some pulmonary infection other than tuberculosis results in calcification and, in addition, the regions where this other disease is prevalent. It was evidence of this nature in the USA that originally led to further studies resulting in clarification of the character and frequency of histoplasmosis infection.

No positive reactions to histoplasmin were found among 463 tuberculosis sanatorium patients tested in France (Rhône department), according to a report which stated that all reactions were " strictement négatives ".[292]

Several hundred residents of the Netherlands were also found to be non-reactors when tested with histoplasmin.[260]

More than 900 university students in Madrid, Spain, were tested with various antigens, including histoplasmin (H-40, 1/1,000); no positive reactions were reported.[365]

In Great Britain, students and Royal Air Force men were examined to determine the relationship between pulmonary calcifications and sensitivity to histoplasmin and tuberculin.[209] At the University of Wales, Cardiff, 82 of 1,188 students were found to have lung calcifications and were tested with histoplasmin prepared in London. Some of the students were tested with 1/1,000 dilution, some with 1/100 dilution, some with both, but none of the 82 reacted to histoplasmin. Furthermore, 62 Royal Air Force men tested with the same dilutions also gave negative results. Nor were any reactors detected in an unpublished study in 1947 of 100 children, aged from 2 to 12 years, tested with histoplasmin (1/1,000) at Guy's Hospital, London.[198]

Absence of allergy was apparent in 320 children tested in Dublin, Ireland.[211]

Although very few large-scale surveys with histoplasmin have been carried out in the Scandinavian countries, the results of several investigations suggest that, if any sensitivity is present, it is probably limited to persons who have been infected abroad. Two studies conducted in Denmark in 1948 with histoplasmin (H-40, 1/1,000) showed no evidence of histoplasmin sensitivity among more than 1,500 persons (WHO Tuberculosis Research Office—unpublished material).

Thirteen patients under treatment from the medical service at Ullevaal Hospital in Oslo, Norway, were tested with histoplasmin (H-40, 2/1,000) early in 1950 (H. J. Ustvedt—personal communication). The reactions were followed very carefully by measuring the size of induration each day after the tests were given. Although most of these patients had small, measurable indurations 2-3 mm in diameter during the first two days, after 72 hours the reactions had faded to essentially nothing. Furthermore, additional tests by the same investigator in almost 100 patients revealed no evidence of histoplasmin sensitivity.

In Finland, 366 general medical patients at the Kivelä Hospital, Helsinki, were tested simultaneously with histoplasmin (H-40, 2/1,000), coccidioidin (1/100), tuberculin (1/1,000), and saline solution.[109] When the reactions were read after four days there were no indurations of 5 mm or more from either fungus antigen, whereas 312 patients were considered positive to tuberculin.

Studies in Czechoslovakia and Poland were made with histoplasmin (H-40, 2/1,000) by members of the International Tuberculosis Campaign in co-operation with the WHO Tuberculosis Research Office (WHO Tuberculosis Research Office—unpublished material).

Among 396 Polish children from 5 to 15 years of age tested in July 1949 in schools of Siedlce, Warsaw province of Poland, 178 girls and 115 boys were reported to have shown no reaction to the antigen ; 103 of the children did not return for reading.

Another group of 586 schoolchildren of comparable age was tested with the same antigen in Cracow during the same month; 552 children (288 girls and 264 boys) were tested, and examined after 48 hours. A seven-year-old boy had a reaction with an induration of 10 mm in diameter; all others were negative.

Similar results were found in Czechoslovakia in August 1949 in testing 550 children and young adults of the district of Ilava. A single reaction was reported among 386 persons who returned for the reading : an eleven-year-old boy had an induration of 4 mm at the site of injection.

Reactions among 989 schoolchildren in Dačice, Moravia, were considered negative, although some small reactions were seen : 52 children had indurations of 1-2 mm, and an eleven-year-old boy had an induration of 4 mm.

Negative reactions were recently reported among 5,000 persons in Roumania tested with histoplasmin (H-42, 1/100) during the early part of 1951 (P. Râmneantu—personal communication).

## Discussion

*Geographical considerations*

An endemic area of histoplasmosis evidenced by numerous cases of the disease and a very high prevalence of histoplasmin reactors is now known to exist in the east-central part of the USA, centring in the lowlands at the junctions of the Missouri, Mississippi, and Ohio rivers. With increasing distance from this centre, the frequency of histoplasmin reactors is progressively reduced. This geographical localization suggests an association of the fungus with large rivers running through relatively low country. Indeed, Beadenkopf & Loosli have recently stated that in a paper to be published they will suggest the possibility that *H. capsulatum* is disseminated in the Mississippi Valley by floods carrying a soil-fungus mixture which is later airborne.[26] In this connexion it is also of interest that Zeidberg et al. published results of a study in Williamson County, Tennessee, showing a relationship between the frequency of histoplasmin reactors and the estimated degree of dampness in the homes investigated.[367]

The distribution of histoplasmin sensitivity in Mexico, Central America, and South America, when viewed geographically, reveals that in general the highest frequency of positive reactors is found in areas not unlike the endemic area in the USA. In Brazil, for example, 30% of a group of schoolchildren were sensitive to histoplasmin in Santarém, which is situated on the bank of the river in the heart of the Amazon Valley. The Paraná river basin in Argentina is another area of fairly high prevalence—over 20% reactors have been reported from the States of Santa Fé and Buenos Aires through which the river flows.

Within these geographical areas there is an indication of an additional point of similarity : with increasing distance from the river and a concomitant increase in altitude, the frequency of histoplasmin reactors tends to be reduced. Such has been found to be the case in the USA. That it may also be true for other countries is suggested, for example, in Argentina by the reduction of sensitivity from 24% along the Paraná river to about 5% in Córdoba in the foothills at the western border of the valley. Similarly, in Mexico the frequency of reactors is high in the States of Yucatán and Chiapas—over 40%; yet several hundred miles north-west in Mexico City, at an altitude of 7,000 feet (2,130 m), there are practically no reactors.

However, there are many exceptions to this apparent relation between geographical factors and the prevalence of sensitivity to histoplasmin. For example, the frequency of reactors is relatively low at either end of the

Mississippi Valley—New Orleans in the south and Minnesota in the north. Nor has histoplasmin sensitivity been observed in any of the large river valleys of Europe, although very few studies have been reported from these areas.

It is apparent that the effort to draw a complete picture of the geographical distribution of histoplasmin sensitivity is seriously handicapped by the lack of sufficient information from many countries. There is obviously a need for more comprehensive surveys which report negative as well as positive findings. From the available reports, however, one might speculate that although a large river moving through low country may provide appropriate environmental conditions, it does not necessarily follow that all such river valleys are endemic areas. Nevertheless, a broad view of the districts where sensitivity is found suggests that priority in the search for new endemic centres might be given to low-altitude regions along large rivers.

*Interpretation of findings*

Evaluation of the reports reviewed in this paper raises the question of cross-reactions which may occur with antigenically related fungi. In this connexion it would seem important for results of histoplasmin-testing to be reported by giving an indication of the size of reactions observed, rather than simply by stating the frequency of " positives ". A reaction classified as " positive " by one investigator might be considered doubtful, or even negative, by another; furthermore, unless the term " positive " is accurately defined, the minimum size of reactions reported as positive is not known by the reader. In addition, although little has been published on the question, if variations in the potency of different preparations of histoplasmin are as great as they are among other skin-testing antigens, the product and the dilution used for testing should be properly identified.

Since reactions to histoplasmin arising as a consequence of infection with other fungi tend to be smaller than those resulting from infection with *H. capsulatum* (C. E. Palmer—unpublished material), a frequency distribution of the size of reactions could be very informative, especially in areas where cases of histoplasmosis are so infrequent that one might be led to suspect other, perhaps still unknown, fungi of being responsible for the histoplasmin reactions. Thus, the finding of even a substantial number of " positive " reactions to histoplasmin, particularly if the reactions are relatively small, may represent cross-reactions. Such is undoubtedly the interpretation to be made of the rather weak histoplasmin reactions observed in California, USA, a known endemic centre of coccidioidomycosis. Also, according to findings recently reported, the histoplasmin reactions found in Honduras and Panama, and possibly in other countries as well, may be analogous to those in California in that they are non-specific for histoplasmosis.

Presumptive evidence for infection by *H. capsulatum* may be afforded by demonstration of a high proportion of strong reactions, particularly in a region where clinical cases of histoplasmosis are known to occur. Complete absence of cases, however, suggests the need for determining the source of the histoplasmin sensititivy by testing with other fungus antigens as well as by a thorough, intensive search for histoplasmosis. The rapidly increasing number of cases now being found in the USA attests the fact that recognition of histoplasmosis through adequate diagnostic facilities presupposes an awareness by clinicians that the disease may occur.

Chest x-rays taken in association with histoplasmin-testing may also provide supplemental evidence for the source of the sensitivity. In the USA, where the most detailed and wide-scale surveys have been conducted, sensitivity to histoplasmin is associated with a high frequency of pulmonary calcification in the endemic area. Thus, it would seem that a fungus other than *H. capsulatum* might be suspected if no calcifications are found among a high proportion of the histoplasmin reactors.

On the other hand, the finding of only very few reactors may serve to rule out the possibility of infection not only by *H. capsulatum* but by related fungi as well. In India, for example, less than 1% of over 1,000 persons tested in Darjeeling, and none of more than 600 tested in Kelur, reacted to histoplasmin. Absence of histoplasmin sensitivity demonstrated by these careful studies rather definitely eliminates the possibility of histoplasmosis and coccidioidomycosis in these areas, as well as other related, but unknown, fungi that may in the future be found to cross-react with histoplasmin. Moreover, from a detailed study of the geographical distribution of histoplasmin sensitivity in the USA, it appears that the frequency of reactors tends to diminish gradually, rather than abruptly, with increasing distance from an endemic centre. Thus, it would seem very probable that further search for histoplasmosis cannot be expected to be fruitful within at least several hundred miles of an area, like Kelur, where no reactors to histoplasmin are found.

Wide discrepancies in the frequency of histoplasmin reactors reported by different investigators in the same area may, in some cases, be the result of tuberculin reactions masquerading as histoplasmin reactions. A cross-reaction between histoplasmin and tuberculin occurs so infrequently as to be negligible,[250] but there is evidence that glassware previously used for tuberculin, even though bacteriologically sterile, may retain enough tuberculin to contaminate the histoplasmin for which it is subsequently used. Thus, one may find tuberculin-sensitive persons with reactions thought to be due to histoplasmin which, in fact, are caused by a relatively small amount of tuberculin remaining in syringes or flasks used for histoplasmin.

**TABLE III. REACTIONS TO MANTOUX 10 TU AND HISTOPLASMIN 1/1,000 TESTS AMONG 631 SCHOOLCHILDREN, KØGE, DENMARK, 1948**

| Histoplasmin 1/1,000 mm induration | Mantoux 10 TU mm induration | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0-5 | | 6-14 | | 15 or more | | Total | |
| | number | %* | number | %* | number | %* | number | %* |
| 0 | 115 | 98.3 | 217 | 95.6 | 211 | 73.5 | 543 | 86.1 |
| 1 - 3 | 2 | 1.7 | 8 | 3.6 | 30 | 10.4 | 40 | 6.3 |
| 4 - 5 | — | — | 1 | 0.4 | 28 | 9.8 | 29 | 4.6 |
| 6 - | — | — | 1 | 0.4 | 18 | 6.3 | 19 | 3.0 |
| Total . . . . . | 117 | 100.0 | 227 | 100.0 | 287 | 100.0 | 631 | 100.0 |

* Percentage of total number of reactors to Mantoux 10 TU tests in each induration-group according to size of reaction to histoplasmin 1/1,000.

This very subtle type of contamination is illustrated in table III by the reactions of 631 Danish schoolchildren tested intradermally with tuberculin and histoplasmin (H-40, 1/1,000) (WHO Tuberculosis Research Office—unpublished material). The stronger histoplasmin reactions occurred only in children who also reacted strongly to tuberculin : in all but 1 of the 19 cases where the induration of the histoplasmin reaction measured more than 5 mm, the tuberculin reaction was more than 15 mm. In no case was a definite reaction to histoplasmin observed in a weak or negative tuberculin reactor. Contamination of the histoplasmin by tuberculin appears to be the only tenable explanation for this finding,[b] as it is highly improbable that sensitivity to histoplasmin would occur only in association with tuberculous infection. It is important to stress the point that had tuberculin-tests not been given at the same time as the histoplasmin-tests, results of this study would undoubtedly have been interpreted as evidence of histoplasmin sensitivity in 3% of the children. Every careful study of histoplasmin sensitivity should be planned to include simultaneous tuberculin-testing, even though technical errors of this type can be avoided through the use of new syringes, needles, and glassware, chemically cleaned with dichromate solution before bacterial sterilization.

Although most of the reported cases of histoplasmosis have been diagnosed in areas known to be endemic for the disease, it is possible that

*b* In another study in the USA, where similar results were observed, it was possible to retest the subjects with histoplasmin dilutions which were prepared, stored, and injected with new equipment. This time, persons who had been histoplasmin-positive to the first test were negative, verifying the evidence for contamination by tuberculin (C. E. Palmer—unpublished material).

some of the isolated cases (and reactors) may be analogous to a case of coccidioidomycosis in Massachusetts, USA, where infection with *Coccidioides immitis* is almost certainly absent.[324] The patient in question was a wool-sorter who developed an acute, fatal illness proved on autopsy to be disseminated coccidioidomycosis. Records in the plant where the man worked showed that a month before the onset of his illness he had spent several weeks sorting a shipment of very dirty, dusty wool from California, an endemic centre of *C. immitis*. This case suggests that similar, important leads regarding the nature of the transmission of histoplasmosis might be furnished by carefully recording details of residence and occupation, in addition to the clinical information usually included in case reports.

*Future research*

In the short period of six years since the first studies were published suggesting the widespread, usually benign nature of histoplasmosis, a tremendous amount of work has been done both in searching for cases of the disease and in testing with histoplasmin. Yet it is obvious that information on the worldwide distribution of infection with *H. capsulatum* is still only preliminary and very incomplete. A relatively rapid and simple way to obtain data pertaining to histoplasmosis, as well as many other diseases, is illustrated by the studies of Grasset and others in Switzerland on large groups of university students and army recruits. Investigations of this nature provide data, representing a cross-section of the entire population for a limited age-group, with which to map out the distribution of histoplasmin sensitivity on a nationwide basis.

At the present time advantage is being taken of such an opportunity in the USA. Studies initiated among student nurses in 1943 by Palmer and his associates have been extended to include over 100,000 young men coming from all parts of the country to the Naval Recruiting Station, San Diego, California. Observations include chest x-rays and skin-tests with coccidioidin, tuberculin, and histoplasmin, as well as a detailed residence history from birth. The results of this programme, integrated with those from other large studies of college students currently in progress, are expected to furnish material for a comprehensive mapping of sensitivity to the several antigens throughout the USA. If similar, large-scale studies were conducted with uniform technique in other countries and the results brought together through international collaboration, significant chapters in the worldwide histoplasmosis story might be written in a relatively short period of time.

## Annex I

## SUGGESTIONS FOR FUTURE STUDIES ON HISTOPLASMIN SENSITIVITY

Attention has been called in this paper to certain problems concerning interpretation of the results of histoplasmin-sensitivity studies reported by different investigators. In view of the need for obtaining data which may be easily compared from place to place, it seems desirable to list several suggestions for conducting surveys which would contribute to greater uniformity and at the same time provide additional, worthwhile information.[c]

Briefly, these suggestions are as follows :

(1) Equipment for histoplasmin, including all glassware, syringes, and needles, if possible, should not have been used previously, or should be chemically cleaned before use with dichromate solution to avoid contamination by tuberculin or other antigens.

(2) Reactions should be carefully palpated and measured, a record being made of the diameters of both erythema and induration.

(3) Tuberculin-tests given simultaneously with histoplasmin, one test in each arm, will often provide critically important observations in connexion with the interpretation of the histoplasmin-tests.

(4) Results would be most informative if reported, not as the percentage positive, but by giving the frequency distribution of the reactions by size of induration. Whether, in addition, the material is grouped according to age, sex, race, occupation, etc., necessarily depends upon the number of persons tested.

(5) Study of pulmonary calcification in the population tested may yield further useful information. To assure objective interpretation of the films, the reader must have no knowledge of the results of the skin-tests. Calcification might be classified into three categories : definite, probable, questionable. The relationship between pulmonary calcification and tuberculin- and histoplasmin-sensitivity may then be presented in summary form simply by showing the frequency of calcification in four groups of persons :

(*a*) Those who react to both antigens (H+ T+)

(*b*) Those who react to histoplasmin but not to tuberculin (H+ T–)

(*c*) Those who react to tuberculin but not to histoplasmin (H– T+)

(*d*) Those who do not react to either antigen (H– T–).

[c] It may be mentioned here that a limited amount of histoplasmin for epidemiological surveys may be obtained by qualified investigators from the Division of Chronic Disease and Tuberculosis of the US Public Health Service, Washington 25, D.C., USA, or through the WHO Tuberculosis Research Office, Scherfigsvej 8, Copenhagen Ø, Denmark.

For a more detailed account of this suggested method for analysis and presentation of data, attention is directed to the paper by Goddard et al. [133] listed in the bibliography.

(6) Since infection by *H. capsulatum* appears to be more closely related to place of residence than to any other factor known today, it is most important to obtain an accurate record of where each person has lived from birth to the time of examination. By using such information to separate the tested population into groups having lifetime residence in restricted geographical areas, endemic centres of histoplasmin sensitivity and, perhaps, of histoplasmosis may be more accurately defined.

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## SUMMARY

Since the long-accepted theory that histoplasmosis is an acute, rare, and fatal disease usually diagnosed after death was first disproved in 1945, increasing interest has been shown by physicians throughout the world in the determination of the prevalence and distribution of this apparently widespread and usually benign infection. From a review of the verified cases of histoplasmosis and the studies on histoplasmin sensitivity to be found in the literature before January 1951, with the addition of a number of hitherto unpublished investigations of histoplasmin sensitivity conducted in various countries throughout the world, the authors have drawn as complete a picture of the world-wide geographical distribution of histoplasmosis and histoplasmin sensitivity as is possible with the incomplete data at present available.

The highest levels of histoplasmin sensitivity in any region in the world occur in the east-central part of the USA near the junctions of the Missouri, Mississippi, and Ohio rivers, an area in which clinical

## RÉSUMÉ

La théorie déjà ancienne selon laquelle l'histoplasmose est une maladie aiguë, rare et mortelle, le plus souvent diagnostiquée après la mort, a subi un premier échec en 1945. Dès lors, les médecins du monde entier ont porté un intérêt toujours croissant à la détermination de la fréquence et de la répartition de cette maladie, qui semble être assez répandue et généralement bénigne. Les auteurs dressent un tableau de la répartition mondiale de l'histoplasmose et de la sensibilité à l'histoplasmine, aussi complet que le permettent les données peu nombreuses dont on dispose actuellement. Ils se fondent sur l'examen de cas certains d'histoplasmose, sur les études relatives à la sensibilité à l'histoplasmine parues dans la littérature avant janvier 1951, ainsi que sur des recherches jusqu'ici non publiées concernant la sensibilité à l'histoplasmine dans plusieurs pays du monde.

Les degrés de la sensibilité à l'histoplasmine les plus élevés, dans le monde, ont été observés dans la partie centrale des Etats-Unis d'Amérique, près des confluents du Missouri, du Mississippi et de

cases of histoplasmosis have been repeatedly observed. In Canada, histoplasmin sensitivity has been found only in the south-eastern provinces. A somewhat lower prevalence of histoplasmin reactors than in the USA has been reported from certain localities in Mexico, Central America, and South America; the relatively small number of histoplasmosis cases diagnosed in these areas is suggestive but inconclusive evidence of the existence of endemic centres of histoplasmosis.

There appears to be very little histoplasmin sensitivity where studies have been conducted outside the Americas. Practically nothing is known concerning sensitivity in Asia, except for two investigations in India which revealed a negligible number of reactors to histoplasmin. A great many reports covering most of the European countries have failed to demonstrate any sensitivity areas, although single, isolated cases of histoplasmosis have been diagnosed in Austria, Bulgaria, England, the Netherlands, Portugal, Spain, and Turkey. Several cases have occurred in the Union of South Africa, which appears to be an area of low prevalence of histoplasmin sensitivity, but little is known of the rest of the African continent. Three cases have been observed in Java, but no studies of histoplasmin sensitivity have yet been reported.

While the evidence is suggestive that large rivers flowing through regions of low altitude provide appropriate environmental conditions for the presence of the fungus, a realistic worldwide picture of histoplasmin sensitivity and naturally-occurring histoplasmosis cannot be completed until extensive investigations have been carried out in areas from which data are still either insufficient, conflicting, or entirely lacking. Student groups and military recruiting programmes provide opportunities for obtaining epidemiological data on histoplasmosis and other diseases rather easily and rapidly on a national basis. If uniform techniques were used, such large-scale, comprehensive studies

l'Ohio, région dans laquelle on a constaté à plusieurs reprises des cas cliniques d'histoplasmose. Une sensibilité à l'histoplasmine n'a été décelée que dans les provinces du sud-est du Canada. Dans certaines localités du Mexique, de l'Amérique centrale et de l'Amérique du Sud, le nombre de sujets réagissant à l'histoplasmine est légèrement moins élevé qu'aux Etats-Unis; le nombre relativement faible de cas d'histoplasmose diagnostiqués dans ces régions laisse supposer mais ne prouve pas l'existence de centres endémiques d'histoplasmose.

Les études effectuées dans d'autres continents semblent indiquer que la sensibilité à l'histoplasmine s'y observe rarement. On ne dispose pratiquement d'aucune donnée pour l'Asie, exception faite de deux enquêtes dans l'Inde qui ont révélé un nombre négligeable de sujets réagissant à l'histoplasmine. De très nombreux rapports concernant les pays européens n'ont pas réussi à démontrer l'existence de régions où cette sensibilité soit très fréquente ; toutefois, des cas individuels isolés d'histoplasmose ont été diagnostiqués en Angleterre, en Autriche, en Bulgarie, en Espagne, aux Pays-Bas, au Portugal et en Turquie. Plusieurs cas se sont produits dans l'Union Sud-Africaine, qui semble être une région où la sensibilité à l'histoplasmine est plutôt rare ; du reste de l'Afrique, on ne sait que peu de chose. Trois cas ont été observés à Java, mais aucune étude sur la sensibilité à l'histoplasmine n'a encore été publiée.

Il est possible que les grands cours d'eau arrosant des régions de basse altitude fournissent des conditions favorables au développement du champignon. Cependant, on ne peut avoir une vue d'ensemble réaliste sur la sensibilité à l'histoplasmine et sur l'histoplasmose rencontrée dans la nature avant que des recherches n'aient été faites dans les régions pour lesquelles les données sont insuffisantes, contradictoires ou inexistantes. L'examen médical de groupes d'étudiants ou de soldats permet d'obtenir facilement et assez rapidement, à l'échelle nationale, des données épidémiologiques sur l'histoplasmose et sur d'autres maladies. Si des techniques uniformes étaient employées, ces études

could provide reliable and internationally comparable data of great value in clarifying the histoplasmosis picture. Suggestions for the conduct of comprehensive histoplasmin-sensitivity studies are given by the authors.

complètes, effectuées sur un grand nombre de sujets, fourniraient des informations sûres et comparables sur le plan international, grâce auxquelles on pourrait se faire une idée d'ensemble plus claire de l'histoplasmose. Les auteurs présentent quelques suggestions pour la conduite de vastes enquêtes sur la sensibilité à l'histoplasmine.

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