20. LANDES, R., REICH, J. AND PERLOW, S.: *J. A. M. A.*, **116**: 2482, 1941.
21. SAKSENA, H. C.: *Brit. M. J.*, **2**: 267, 1943.
22. MARSHALL, E. A.: *Am. J. Clin. Path.*, **9**: 298, 1939.
23. COOGAN, T., MARTINSON, D. AND MATTHEWS, W.: *Illinois Med. J.*, **87**: 296, 1945.
24. ZOHMAN, B. AND SILVERMAN, E.: *Ann. Int. Med.*, **16**: 1233, 1942.
25. FIELD, W. W.: *Am. J. Med.*, **4**: 154, 1948.
26. SLADE, J.: *New England J. Med.*, **234**: 753, 1946.
27. SCHNEIDER, T. AND MICHELSON, D.: *South African M. J.*, **2**: 57, 1947.
28. DAVIDSOHN, I.: *J. A. M. A.*, **108**: 289, 1937.
29. GELIEBTER, S.: *Lancet*, **2**: 753, 1946.
30. CUSTER, R. AND SMITH, E.: *Blood*, **3**: 830, 1948.
31. FLEDELIUS, M.: *Acta Ophth.*, **13**: 150, 1935.
32. SUCHER, A. AND SWARTZ, E.: *Wein. klin. Wchnschr.*, **49**: 1417, 1936.
33. GSELL, O.: *Deutsche med. Wchnschr.*, **63**: 1759, 1937.
34. SCHMIDT, V. AND NYFELDT, A.: *Acta Oto-laryng.*, **26**: 680, 1938.
35. HUBER, W.: *Schweiz. med. Schnschr.*, **68**: 892, 1938.
36. PIETZONKA, H.: *Deutch. Arch. f. klin. Med.*, **185**: 153, 1939.
37. WERLIN, S., DOLGOPOL, V. AND STERN, M.: *Am. J. M. Sc.*, **201**: 474, 1941.
38. RICHARDSON, J. S.: *Lancet*, **1**: 618, 1942.
39. HILLER, R. AND FOX, M.: *Marquette Med. Rev.*, **7**: 152, 1943.
40. BERCEL, N. A.: *J. Nerv. & Ment. Dis.*, **107**: 537, 1948.

PULMONARY CALCIFICATION AND HISTOPLASMIN SENSITIVITY

Paul Green, B.A., M.D.

Assistant Director Laboratories, Deer Lodge Hospital, D.V.A., Lecturer in Medicine, University of Manitoba Medical College, Winnipeg, Man.

IN 1906 Darling,[1] working in the Panama Canal Zone, encountered at autopsy cases of what appeared to be kala-azar, a disease which had not been reported from the western hemisphere. Closer study of the apparent causative organism in these cases disclosed differences between it and that which was found in kala-azar. Darling therefore felt that he was dealing with a different and previously undescribed disease. He considered the organism to be a protozoan, and called it *Histoplasma capsulatum*, and the disease histoplasmosis.

It was accepted that Darling had indeed described a new disease, but because it seemed to be a very rare tropical disease, little general interest was shown in it. In 1926 Watson and Riley encountered a case in Minnesota, the first case to be reported from the United States proper. By 1937 only 13 cases had been recognized, and the disease was still regarded as an uniformly fatal medical curiosity. DeMonbreum in 1934 restudied the organism which he isolated from a fatal case, and showed that it was a fungus and not a protozoan.

Since 1937 more and more cases have been reported and by 1946 88 cases were gleaned from the literature. Most of these were encountered in the United States, but some had also been reported from other areas. It was also recognized that the disease was not uniformly fatal.

In 1941 Zarafonetis and Lindberg[2] prepared antigens from cultures of the *H. capsulatum* and used this "histoplasmin" to determine the incidence of skin sensitivity in the same manner as tuberculin is used to determine tuberculin skin sensitivity. In surveys of positive histoplasmin skin sensitivity it was discovered that there were striking geographical differences.[3, 4] In the Mississippi basin a very high incidence of positive reactors was found, and the incidence of positive skin reactors tended to diminish the further from this region that testing was done. However, occasional pockets of increased incidence of histoplasmin sensitivity are encountered.

It had been known for many years that the incidence of pulmonary calcification as detected by x-ray films of chests also varied geographically. Thus in American Army recruits the incidence of calcification varied from 6% of inductees in Oregon to 28% in Kentucky.[5] In most regions it had been assumed that pulmonary calcification was evidence of old tuberculosis infection, and indeed some inductees with marked pulmonary calcification were rejected on this ground. It was also known that many of these individuals were negative reactors to tuberculin, but this was explained on the gradual loss of tuberculin sensitivity as the individual became older. However it has been shown[6] that tuberculin skin sensitivity is lost very slowly, and this is probably true particularly in urban areas where repeated contact with tuberculosis is likely.

Great interest was evidenced, therefore, when it was shown[7, 8, 9] that the incidence of pulmonary calcification showed a much closer relationship to positive histoplasmin skin sensitivity than to positive tuberculin skin sensitivity. It therefore appeared likely that pulmonary calcification was not necessarily evidence of old tuberculosis, but in certain areas at least, represented old histoplasmosis.

The next step was to demonstrate that infection with *Histoplasma* could produce this picture, and that recovery could occur, leaving calcified nodules that could be detected by x-ray. This has been done. Sontag and Allen[10] observed school children who were histoplasmin and tuberculin negative, and who had negative

chest plates. Some of these later developed x-ray evidence of infiltrative lesions in their lungs, whose appearance coincided with the appearance of positive skin reaction to histoplasmin, but still negative to tuberculin. These lesions eventually became calcified, and skin sensitivity to histoplasmin remained, whereas skin sensitivity to tuberculin did not appear. Similar observations have been made by Furcolow.[11] In some of these cases additional evidence was the isolation of *H. capsulatum* from tonsils and gastric washings.

It therefore appears to be established that histoplasmosis is not an uniformly fatal disease, but on the contrary, is most often a very benign disease. It also appears established that pulmonary calcification need not be evidence of old tuberculosis, but may be evidence of other types of infection, particularly histoplasmosis.

PURPOSE OF PRESENT INVESTIGATIONS

At the time that this investigation was undertaken, no surveys had been reported from Canada. Dr. C. B. Stewart has carried out tests on a number of students at Dalhousie.[12] He did not find any positive reactors in those who came from the Maritimes and Newfoundland, but did find some positive reactors in a few individuals from the United States, Southern Ontario and the British West Indies, as well as in a few veterans who had travelled widely. The findings of Heaton[12a] are similar to those that we have observed, except that the incidence of pulmonary calcification in this group was only one-tenth the incidence in our group.

Surveys have been reported recently from Quebec[13, 14] where a much greater incidence of positive reactors was found in the southern part of the province than in the northern part. This suggests that the St. Lawrence basin may be an endemic area for histoplasmosis. Our purpose was to determine how frequently one encountered skin sensitivity to histoplasmin in veterans of this region, and to see if there was any correlation between the skin sensitivity here and the incidence of pulmonary calcification. Interestingly enough, after this survey was begun a fatal case of histoplasmosis was encountered by Dr. Lederman[15] in this city. We encountered one case which may have been an acute pulmonary histoplasmosis in this hospital, and a brief history of this individual is appended.

Selection of material.—440 individuals were included in the survey. These were veterans admitted to Deer Lodge Hospital medical services. Their ages ranged from 18 to 82. All but twelve were males. This group, therefore, cannot be considered unselected; they have been selected by sex, age, physical fitness for the armed services at one time, they have been admitted for medical rather than surgical reasons and, finally, they are a group that has travelled extensively.

Procedure.—Chest films were taken of each individual. A tuberculin skin test with 1/1,000 dilution of tuberculin as supplied by the Central Tuberculosis Clinic in Winnipeg, was done and read in the usual manner. A histoplasmin skin test was done on the other arm at the same time with 1/100 dilution of histoplasmin, which was graciously supplied by the Eli Lilly Co. This test was read and interpreted in the same manner as the tuberculin reaction—both were read in 48 hours and an area of erythema of 1 cm. or more in diameter was considered a positive test.

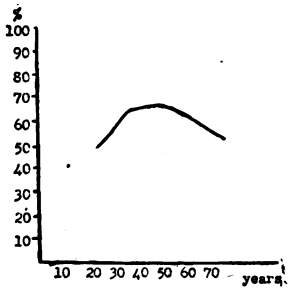

Fig. 1

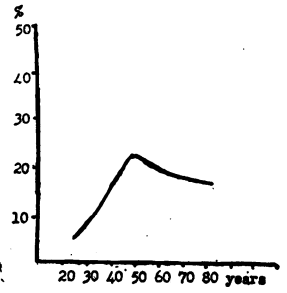

Fig. 2

Results.—258 cases reacted positively to tuberculin (59%). In order to determine whether there was a tendency for the incidence of positive tuberculin reactors to decrease with age the group was split into decades and the incidence of positive reactors, in percentage of each decade, was determined. The distribution is plotted in Fig. 1. This curve indicates that there was an increasing percentage of positive tuberculin reactors up to the 40 to 50 year old group, and then the incidence tended to fall off. However, on plotting the incidence of pulmonary calcification in a similar manner (Fig. 2) a similar type of curve was produced. As it is doubtful that pulmonary calcifications ever disappear, it seems probable that some other factors may be present in the 40 to 50 age group present in this series, and that the percentage of positive tuberculin reactors in

this group is perhaps out of proportion to what might be expected from random sampling.

Twenty-three cases (5.2%) had positive skin tests to histoplasmin. Of these, 15 (65%) also had positive tuberculin skin tests, which is near the incidence for the whole group. Of this group of positive histoplasmin reactors four had lived in areas known to be associated with a high incidence of positive histoplasmin skin reactions (Mississippi basin). Five had never been outside of Canada, but had been in Eastern Canada at some time. The remaining 14 cases had been in Northwest Europe, and one had also been in Hong Kong. No survey has been reported from the Hong Kong area. However, surveys from Northwest Europe[16, 17, 18] have not shown a very high incidence of positive reactions to histoplasmin skin tests.

The incidence of pulmonary calcification as determined by chest x-ray for the whole group was 61 cases (14%); 47 of these had positive skin tests for tuberculin, or 17% of the positive tuberculin reactors had pulmonary calcification; 8% of the negative reactors to 1/1,000 tuberculin had pulmonary calcification.

Positive histoplasmin reactors.—While there were not enough individuals in this group to be statistically significant, the age distribution was scattered and did not tend to be in any particular age group. Of this whole group 14 cases (61%) had pulmonary calcification. This is significantly greater than the incidence of pulmonary calcification in the whole group. Five out of the 8 cases that were histoplasmin positive but tuberculin negative had calcification, an incidence about the same as for the whole group of histoplasmin positive individuals. It was noted that the type of calcification tended to be different in this group, as compared with the histoplasmin negative group that had pulmonary calcification. This latter group tended to have isolated calcification in the lung periphery with often a large area of calcification at the hilum. The histoplasmin positive group tended to have multiple small areas of calcification scattered throughout the lung. Often the x-ray picture of the lungs tended to show a rather fine, reticulated appearance. Of the group of positive histoplasmin reactors, 9 had this scattered type of calcification. Of the group of negative reactors to histoplasmin only two had multiple calcified shadows, and one of these was a negative tuberculin reactor as well.

The appearance of these chest films had probably given rise, in the past, to the diagnosis of "healed miliary tuberculosis" that is sometimes encountered in radiological reports. The radiologists in this hospital now recognize that this picture is very suggestive of histoplasmosis. Since this survey was completed they have referred three cases of skin tests on the basis of such an x-ray film, and all three cases have had a positive skin reaction to histoplasmin. A photograph of a typical chest film is reproduced in Fig. 3.

The results of the survey are tabulated in Table I.

TABLE I.

Tuberculin	negative	negative	positive	positive
Histoplasmin	negative	positive	negative	positive
Calcification	9/174 (5%)	5/8 (63%)	39/243 (16%)	8/15 (53%)

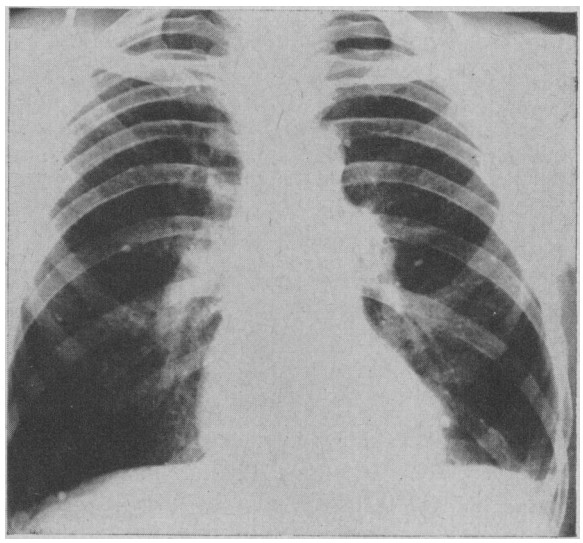

Fig. 3

These results confirm the observations previously made[7, 8, 9] that the incidence of pulmonary calcification is much higher in those that have positive skin reactions to histoplasmin than those that have positive skin reactions to tuberculin but negative reactions to histoplasmin.

CASE HISTORY

The patient was a 24-year old male who always had lived in Manitoba, but had visited Southern Ontario just prior to the onset of his present illness. He had always been well. A chest film taken in 1946 was negative. In February, 1948, he complained of general malaise and some discomfort in his left chest, made worse by breathing, but not severe. He was in bed at home for ten days, and then returned to work, as he felt better.

On May 15, 1948, he again noticed this pain in his left chest, aggravated by breathing, and again noticed that he was feverish and feeling unwell. He had no cough. A chest x-ray was taken and showed enlargement of the left hilar area, and minute shadows in both mid-lung fields, rather soft in appearance. He was admitted to hospital.

His hæmoglobin was 100% (15.6 gm. %), white cell count was 10,000, with a differential of 69% polymorphonuclears, 29% lymphocytes, 1% monocytes and 1% eosinophiles. His sedimentation rate (Westigren) was 25 mm./hr. Urine was normal. His blood picture did not change appreciably during his illness but his sedimentation rate increased to a maximum of 95 mm./hr. and then gradually returned to normal.

For four weeks he had a daily fever, up to a maximum of 101° F. General physical examination was negative throughout his period of observation. X-rays of his bones did not reveal any abnormalities. Repeated cultures of gastric washing were negative for tubercle bacilli. Unfortunately, repeated cultures for fungi were not done, and one that was done did not grow any fungi. Serum proteins were found to be: albumin 4.3 gm. %; globulin 2.2 gm. %; total 6.5 gm. %. His histoplasmin skin test was very strongly positive. Repeated tuberculin skin tests, done at intervals over the following year, remained negative, even in 1/100 dilution. Bronchoscopy was negative. Sternal puncture did not reveal any gross abnormalities. His course was progressively upward. The pain in his chest disappeared after 48 hours. His temperature gradually returned to normal, and he regained the few pounds in weight that he had lost.

When reviewed in August, 1949, he felt well. Blood was normal. X-ray of his chest showed that there was still some increase in the size of the hilar shadows. The scattered small shadows throughout the lungs, and seen particularly in the mid-lung zones, were much harder in appearance.

While this case cannot be considered to be a proved pulmonary histoplasmosis, because of the failure to recover the organism, circumstantial evidence would favour such a view.

DISCUSSION

These results indicate that in veterans, the incidence of positive reactors to histoplasmin in this area is about 5%. This figure is similar to the figure reported in Minnesota, immediately south of the border in this region.[19] However as this group was a widely travelled group, and therefore probably had a greater chance of becoming histoplasmin positive no conclusions can be drawn as to the incidence of positive reactors to histoplasmin in the general civilian population of this area. It should not be greater, however.

Pulmonary calcification as seen on a chest plate, therefore, need not be considered indicative of previous infection with tuberculosis. However, in this region it most likely is an indication of previous tuberculosis infection. If the calcification tends to be scattered and composed of fine shadows, it is more likely to be associated with a positive histoplasmin skin reaction and, presumably, indicative of previous infection with *H. capsulatum*.

SUMMARY

In a group of 440 veterans in Manitoba, many of whom had travelled widely during war service, the incidence of positive skin reactions to 1/1,000 tuberculin was 59%. The incidence of positive skin reactions to 1/100 histoplasmin was 5%. The incidence of pulmonary calcification as determined by x-ray of the chest was 14% for the whole group. In those who did not react to either tuberculin or histoplasmin in these dilutions, the incidence of calcification was 5%; of those who were tuberculin positive and histoplasmin negative the incidence of pulmonary calcification was 15%; in those who were tuberculin negative and histoplasmin positive the incidence was 63%, and in those who were tuberculin positive and histoplasmin positive 53%. There is a brief discussion of the significance of these findings.

I wish to express my thanks to Dr. J. D. Adamson, whose supervision and advice has been invaluable; and to thank Mrs. Olive Glover, who did the skin testing in the survey.

REFERENCES

1. DARLING, S. T.: *J. A. M. A.*, **46**: 1283, 1906.
2. ZARAFONETIS, C. AND LINDBERG, R. B.: *Hosp. Bull. Ann Arbor*, **7**: 47, 1941.
3. PALMER, C. E.: *Pub. Health Rep., Wash.*, **61**: 475, 1946.
4. FURCOLOW, M. L., HIGH, R. H. AND ALLEN, M. F.: *Pub. Health Rep., Wash.*, **62**: 1711, 1947.
5. LONG, E. R. AND STEARNS, W. H.: *Radiology*, **41**: 144, 1940.
6. DAHLSTROM, A. W.: *Am. Rev. Tuberc.*, **42**: 471, 1941.
7. CHRISTIE, A. AND PETERSON, J. C.: *Am. J. Pub. Health*, **35**: 1131, 1945.
8. HIGH, R. H., ZWERLING, H. B. AND FURCOLOW, M. L.: *Pub. Health Rep., Wash.*, **62**: 631, 1947.
9. ZWERLING, H. B. AND PALMER, C. E.: *Radiology*, **47**: 59, 1946.
10. SONTAG, L. U. AND ALLEN, J. E.: *J. Pediat.*, **30**: 657, 1947.
11. FURCOLOW, M. L.: *Pub. Health Rep., Wash.*, **64**: 1363, 1949.
12. STEWART, C. B.: Personal communication.
12a. HEATON, T. G.: *Canad M. A. J.*, **62**: 252, 1950.
13. GUY, R., ROY, O., POUPART, G. AND PANISSET, M.: *Canad. J. Pub. Health*, **40**: 306, 1949.
14. GUY, R., PANISSET, M. AND FRAPPIER, A.: *Canad. J. Pub. Health*, **40**: 306, 1949.
15. LEDERMAN, J.: Personal communication.
16. A Survey with Histoplasmin in Dublin: *J. Med. Assoc. Eire*, **19**: 162, 1946.
17. MCCRACHE, B. H.: *Thorax*, **5**: 45, 1948.
18. KOLLER, F. AND KUH, H.: *Schweiz. Med. Wochen.*, **78**: 1077, 1948.
19. CHRISTIE, A. AND PETERSON, J. C.: *J. A. M. A.*, **131**: 658, 1946.

A man lives not only his personal life as an individual, but also, consciously or unconsciously, the life of his epoch and his contemporaries.—Thomas Mann.