June 4, 1951

Dr. S. B. Salvin
Rocky Mountain Laboratory
Hamilton, Montana

Dear Dr. Salvin:

I am writing to you because in my opinion you have published the best work on complement fixation with histoplasmin, and I would greatly appreciate your comments and advice on a problem which I have recently encountered.

In 1947 we had an epidemic in Cincinnati of what we called "miliary granulomatous pneumonitis" in a group of 12 men who cleaned out a tower full of pigeon excreta. At that time, no etiological diagnosis was made although a number of possible agents were investigated serologically and by skin tests. The serological tests carried out in 1947 were negative for ornithosis, "Q" fever and toxoplasmosis. Skin tests carried out 3 months after onset were negative for coccidioidomycosis and blastomycosis. At 3 months the tests with histoplasmin yielded erythema without induration after 24 to 48 hours, and upon repetition of the tests 5 months after onset all were negative with the 1:1000 dilution of histoplasmin and only 3 were positive with the 1:100 dilution of histoplasmin. Accordingly, at that time we did not regard histoplasma as an etiological agent for this condition. We had a series of acute and convalescent serum specimens frozen away on these patients and during the past few months, after considerable discussion with Dr. Furcolow, these sera were tested for complement fixation with histoplasmin by Dr. Schubert. I am enclosing a copy of the results that were obtained.

You will notice that at least 9 of the patients yielded positive results at 3 to 4 weeks after onset with titers varying from undiluted to 1:64. You will also notice — and this is the crux of the problem that concerns me here — that at 6 months after onset the high titers disappeared and the sera were positive either only in the undiluted state or not at all. I have tried to find out from Dr. Furcolow what his experience had been with patients with proved histoplasmosis infection, but unfortunately, he had data only on undiluted serum tested with the histoplasmin antigen. Even so, it appeared from his data that only approximately 70 per cent gave positive complement fixation tests with histoplasmin at 3 to 5 months after onset and that at 10 to 16 months, only 40 per cent gave positive reactions...
with undiluted serum. However, in several recent reports on complement fixation tests with yeast phase antigen, fairly high titers were reported in patients approximately 6 months after onset, and in one group, reported by White and Hill (American Review of Tuberculosis, 1950, 62, 1), a number of patients tested 9 to 11 years after onset of their illness yielded C-F titers with yeast phase antigen in the range of 15-150. In view of the negative skin tests in our patients at 5 months after onset and the rapidly dropping C-F titers with histoplasmin, it seemed to me that they might have been infected with a fungus that is related to histoplasma rather than with histoplasma itself. It may also be worthy of note that a recent check up, 4 years after onset, revealed no calcification in the lungs of our patients.

What I would particularly like to learn from you is the following:

1. Have you experience with human sera (as well as other sera) that the titers with yeast phase antigen are higher and persist longer than with histoplasmin in proved cases of histoplasma infection?

2. In your opinion, are the results obtained on the Cincinnati group of patients more compatible with an infection caused by another fungus related to histoplasma than with histoplasma itself?

3. Have you any data which might indicate that the inoculation of large amounts of penicillin, particularly in the crude form in which it was available in 1947, might give rise to C-F antibodies which would cross with histoplasmin? All of our patients received very large doses of penicillin.

4. Would you consider it worthwhile to check some of the 6-months sera, which gave negligible or negative results with histoplasmin, in tests with the yeast phase antigen? I still have some of those sera available in the frozen state and would be very glad to send them wherever you might suggest that the tests with yeast phase antigen would be carried out most reliably.

I would also be deeply grateful to you for any comments that you might care to make about the problem of complement fixation in histoplasmosis and related fungal infections.

With many thanks,

Sincerely yours,

Albert B. Sabin, M. D.