

April 18, 1929.

My dear Doctor Cunningham:

Your letter about the meetings at Atlantic City has just come. First let me say that there can be no conflict between our groups because all we both want is to get at the truth, and we certainly realize that there may be many shifts in opinion before we finally arrive at any view that will really hold water.

It is entirely clear that the epithelioid cell is not the exclusive reaction of tuberculosis. The old guard pathologists knew that, as is evidenced by the definition of "tubercular", meaning lesions like the "tuberculous". Doctor Forkner has found the occasional epithelioid cell in the typical supravital reaction in normal peripheral lymph nodes of rabbits; they occur in the septa of tumors, not to mention other well-known pathological lesions in the old group of the infectious granulomata. What we have been working on is not the exclusive production of epithelioids by the tubercle bacillus and its fractions, but rather to determine which of the substances isolated from the bacillus can and which cannot produce epithelioid cells. This we think we have determined pretty satisfactorily. There may still, of course, be some slip in our results but we feel fairly content at the present time that the lesions are produced by the lipid fractions instead of by the proteins or the carbohydrates. It is our opinion that the epithelioid cell may be produced by some substance which can be broken up in the cell into very fine particles, or which is taken in by the cell in a very finely divided state, which accounts for the tiny bodies that react to neutral red in the rosette; that it is probable that the cell is unable to change this substance with any degree of rapidity. For example, the immediate reaction to the phospholipin seems to be its phagocytosis by cells which are probably of the clasmatocyte type; the phosphatid undergoes a change in these cells with considerable rapidity, since this reaction disappears certainly in a week's time, whereas the epithelioids which then appear can persist in an apparently unchanged form for a period of five months at least. By this time, of course, many of them have disappeared, but many still remain exactly as they appear when first formed. Of course one phase of the problem is: Is there any common chemical factor which can produce this type of cell, or is the common factor the inability of the cell to change or digest certain substances which have no common structural formula? This problem is distinct from the one which we are reporting at the present time, namely, just what part of the fractions from the bacillus, or what substances the chemist can isolate do produce the lesions?

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Doctor White's problem is not to present all the scientific aspects of the problem, but to give to an audience probably quite largely hostile to his program such an interesting presentation of the work as to capture their minds and make them for the moment forget that the plan was not originated by them. For example, one of them has said quite freely that he did not see why Doctor White had asked a group who know nothing whatever about tuberculosis, when there were plenty of pathologists in the country who know everything that had ever been done. Naturally, Doctor White wants to make the group sufficiently favorable by capturing their intellectual interest enough so that they will not keep on trying to block him in his efforts to make a really big undertaking go through.

To return to my original ideas, in studying cells physiologically, one has to consider first chemical substances which they take in and can synthesize into more complex substances; second, substances which they take in and can break down into simpler substances, and third, substances which they can take in but which they are not differentiated toward dealing with. Of course the experiments, such as those with trypan blue, involve using a substance entirely foreign to the possible physiology of the cell. Carbon, however, is a comparable substance which is met with physiologically. Our problem is to try to find out in which of these three groups of substances the material that produces epithelioids belongs. We are not yet far enough along with this type analysis to begin to talk about it.

It seems to me that it will be better all round if you discuss our work at the meetings, bringing in your work if the ideas involved can be made clear with reference to ours and not bringing yours in if it cannot be made to bear on the questions involved. We will see you before hand and show you our lantern slides and go over what we are going to say. We shall present the material from the standpoint of which elements in the lipid fractions produce lesions that in the microscopic sections look like those that the pathologist regards as actually diagnostic and those which he regards as atypical. We are greatly interested in pinning down the pathologists into defining a tubercle; it all boils down to the fact that they consider a tubercle a tubercle when they can stain tubercle bacilli in it. We find great variety in the lesions; considering the epithelioid cell and giant cell as the units we produce every possible permutation and combination, massive and diffuse, in clumps, in masses, and scattered, pure epithelioids, pure giant cells and mixed. These types vary somewhat with the different fractions. Have you followed all your reactions through in fixed sections; that is, to our mind, a very important part of the evidence, and we have found that the more we study the sections the more we want fuller and fuller notes and studies of the fresh.

I could make this letter much better if I rewrote it, but there isn't time and I guess that you can work out what I mean. I am going to Washington for the National Academy meetings next week and will have a long talk with White and explain your position to him. If I understand

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his problem, it will please him most to have you discuss our work with the idea of getting a few ideas clearly before the Association, rather than opening up the whole still vague subject of the general reactions of cells.

Cordially yours,

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