MECHANISM OF ACTION OF THE SULFONES

To The Editor:

I was interested in reading "The Mechanism of Action of the Sulfone Derivatives in Lepromatous Leprosy," by Drs. Paulo Rath de Souza and Moacir de Souza Lima, reprinted in the July-September issue of THE JOURNAL last year. They state that the action is probably on some mechanism which they call the "Virchow cell-Hansen bacillus complex," and that "the sulfones. . . . act principally on the Virchow cell component, altering in some way its metabolism and rendering its cytoplasm unsuitable for multiplication and survival of the bacillus," although they do not deny a bacteriolytic effect of sulfones.

I believe these observations are important, particularly since Hanks has been able to show that the bacillus of human leprosy and Stefansky's bacillus thrive and multiply inside the histiocytes (macrophages) in tissue culture as long as the cells are not destroyed. When the bacilli multiply and subsequently

destroy the cells, they are liberated into the extracellular substance where they are inhibited or destroyed and the infection diminishes. Cochrane reports that the leprosy bacilli appear more frequently in the extracellular spaces after sulfonization, so that the observation of the authors referred to above, that the histiocyte is necessary for the intracellular growth and multiplication of leprosy bacilli, gains importance.

A similar observation has been made in work on the vaccinia virus at the Yale Medical School. In tissue culture the virus multiplies well when inside the cells, but when the growth is such that the cells are destroyed and the organisms are set free in the extracellular fluid, they are destroyed and are unable to penetrate new cells. Further work has shown that a mucoprotein, hyaluronic acid, causes this inhibition; when the mucoprotein is removed from the substrate of the tissue culture, the vaccinia virus is able to break out of the cells and thus continue to multiply.

The findings of Hanks that certain sera of animals have a similar inhibitory effect on rat leprosy bacilli may fit into the concept of the Virchow cell-Hansen bacillus complex. To summarize, we might hypothesize that the sulfones disturb the Virchow cell in some way, causing the bacilli to break out into the extracellular substance, where they are inhibited by the muco- or lipoproteins.

There is another interesting observation to the effect that, by some factor of heredity, the colloids (mucoproteins) may not be produced in equal amounts in all persons. A group studying urine colloids in patients with persistent renal calculi have found that in over 90 per cent of the cases the colloids are lower than normal, with a resulting lowering of urinary surface tension. Renal stones are thus easily developed because the micella of the stones can easily form concretions of phosphates and oxalates.

If this be the case, a similar hereditary deficiency in production of colloids might be considered in leprosy cases. The bacilli, entering the body through the skin, are able to get into the histiocytes where they can multiply, instead of being inhibited or destroyed by the colloids in the extracellular ground substance. (See Hanks, J. H., Metabolic inhibition of *Mycobacterium leprae murium* by serum components which modify the hemagglutination or infectiousness of certain viruses. Bact. Proc., Soc. American Bacteriologists, 1952, p. 99.)

Persons with habitual renal calculi have abnormally low

urinary colloids. When given hyaluronidase subcutaneously, the production of urine colloids is elevated sufficiently to prevent the formation of new renal stones. If it should be established that persons with leprosy are deficient in extracellular colloidal substances, it would be interesting to see if our present treatment with sulfones could be further improved by increasing this colloid level. The sulfones are supposedly instrumental in bringing the leprosy bacilli out of the cells into the extracellular ground substance, where a high lipo- mucoprotein content would cause greater inhibition or destruction of them.

Much of the foregoing is based on theory, and there is assumed a close similarity between rat and human leprosy which may not exist; but, as Rath de Souza and de Souza Lima have quoted from Selye, "even incorrect theories are often of great help in unveiling the secrets of nature, as long as we regard them merely as concrete formulations of possibilities, which, by virtue of their concreteness, lend themselves to be proven or disproven by subsequent observation."

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TO THE EDITOR:

I have gone through the interesting article "The Mechanism of Action of the Sulfone Derivatives in Lepromatous Leprosy" by Paulo Rath de Souza and Moacir de Souza Lima. In it the following statements have been made:

"The biology of the Hansen bacillus indicates that it depends strictly on the Virchow cell in order to live and multiply successfully."

"The sulfones act principally on the Virchow cell component [of what they call the Virchow cell-Hansen bacillus complex], in some way altering its metabolism and making its cytoplasm unsuitable for the life of the Hansen bacillus."

In a lepromatous case bacilli are found in Virchow cells and also outside them. In such a case if Hansen's bacillus depends strictly on the Virchow cells in order to live and multiply successfully, and if sulfones act principally on the Virchow cell component making its cytoplasm unsuitable for the life of the Hansen's bacillus, we fail to explain how in the same case bacilli live and multiply outside Virchow cells and how they disintegrate under sulfone treatment.

Bacilli are also found in some tuberculoid and other neural cases where there are no Virchow cells. Therefore, if we scrutinize the above statements and apply them in a larger con-

text we fail to explain how, in the absence of Virchow cells, a bacteriologically negative neural case becomes positive or positivity in the same case increases and how these bacilli disintegrate under sulfone treatment.

It seems, therefore, that bacilli are nourished by the tissue fluid in general of a leprous lesion and not by Virchow cells alone, and that alteration of metabolism in the tissues due to sulfone treatment is more general and not limited to the Virchow cells, thus making the tissues unsuitable for the growth and multiplication of bacilli anywhere in the lesion.

I agree with the statement that, "An identical mechanism is also operative, although not so regularly or effectively, either when other ways of treatment are applied or in natural condition when regression of the lesions occur without treatment."

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