IN THE MEANTIME. . . .

In this department of our last issue [1] we discussed reports which emphasize the need for more intensive study of the physiology and biochemistry of the mycobacterium which is the causative agent of leprosy.[2, 3]

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[1] EDITORIAL. Intracellular parasitism of mycobacteria; Suter's review, and Hanks' commentary. THE JOURNAL **22** (1954) 81-85.

[2] SUTER, E. Some aspects of intracellular parasitism of pathogenic microorganisms; a review. THE JOURNAL **22** (1954) 1-11.

[3] HANKS, J. H. The implications of Suter's review of intracellular parasitism with respect to the problem of leprosy. THE JOURNAL **22** (1954) 12-15.

The difficulties of the problem of attaining an effective therapy for this disease are greatly aggravated because, as yet, the germ cannot be cultivated and the infection cannot be reproduced in animals. For this reason, every possible approach should be investigated thoroughly, even if for some things it would be necessary to work with a mycobacterium which is not the Hansen bacillus at all, however many of its attributes it may exhibit.

Important victories in the general field of chemotherapy have been won in recent years by the empirical method of trial and elimination, but the situation with other bacterial diseases is not as bad as with leprosy because the preliminary steps in the processing of a new drug can be carried out in the laboratory, by *in vitro* and *in vivo* tests. One important advance, and only one, has been made in leprosy as a result of the application of a drug, Promin, which had been tried out in tuberculosis—and which, incidentally, had been found wanting for that disease. The sulfone group which it represents is the best thing that has happened yet in leprosy, but how far it is from what is really needed is common knowledge.

In a recent paper read when he was awarded the Dearbolt Medal, Dr. Wm. H. Feldman of the Mayo Clinic gives a most interesting informal account of how he and his clinical associate, Dr. H. Corwin Hinshaw, had led the way to the use of streptomycin in tuberculosis.[4] He pointed out that the investigation of the chemotherapy of tuberculosis had really begun several years before streptomycin was discovered, first with many of the sulfonamides and then with Promin, shortly after it was produced in the Parke, Davis laboratories. The first results in guinea-pig tuberculosis "were exciting and could not be ignored." [5] There then followed an extensive and prolonged study of the sulfones, clinical as well as experimental.[6] Despite the scepticism of many people, certain of these compounds proved highly effective in experimental tuberculosis, but in clinical trials Promin revealed shortcomings that indicated that their triumph was incomplete.

Historically, Feldman points out, Promin is of significance because it "was the first antimicrobial substance which was proved unequivocally effective in suppressing an experimental tuberculous infection induced by the human-type tubercle bacillus." Then followed—more or less by chance —the trial of Promin at Carville which, with Muir shortly afterward working with Diasone in Trinidad, has changed the situation in leprosy so greatly. For tuberculosis, attention turned to streptomycin, by steps which are the main feature of Dr. Feldman's talk, and since then scant

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[4] FELDMAN, W. H. Streptomycin: Some historical aspects of its development as a chemotherapeutic agent in tuberculosis. *American Rev. Tuberc.* **69** (1954) 859-868.

[5] FELDMAN, W. H., HINSHAW, H. C. and MOSES, H. E. The effect of Promin (sodium salt of *p,p'*-diamino-diphenyl-sulfone-N,N'-dextrose sulfonate) on experimental tuberculosis: A preliminary report. *Proc. Staff Meet., Mayo Clinic* **15** (1940) 695.

[6] FELDMAN, W. H. An evaluation of the efficacy in tuberculosis of sulfonamides, sulfones and certain other substances. *J. Roy. Inst. Publ. Hlth. & Hyg.* **9** (1946) 297.

attention has been given the sulfones in clinical tuberculosis. In ending his talk, he pointed out:

. . . . that the development of streptomycin in the therapeusis of tuberculosis, like the development of other successful chemotherapeutic agents, was not the result of a carefully planned attack based on a knowledge of the vulnerable biochemical factors of the tubercle bacillus either *in vitro* or *in vivo*. Instead, the approach was entirely empirical, based on the assumption that all microbial life is susceptible to antagonistic factors of varying physical and chemical characteristics.

In the absence of sufficient, precise information regarding the intrinsic mechanisms on which microbial life is dependent, it has not been possible in the search for new microbial antagonists to devise, by chemical manipulation, a predictable, effective, nontoxic substance whose performance *in vivo* will meet successfully the exacting requirements of an antimicrobial agent against a specific pathogenic microorganism.

A thorough knowledge of the disease and the application of systematic, reliable, and tedious methods of experimental pathology are prerequisites for the successful search for new antimicrobial substance. However, despite the refinements of methods and the most diligent devotion to the task, the finding of new bacterial antagonists has been dependent largely on chance rather than on science.

It would be highly gratifying intellectually to have it said that our attack on the problem of specific chemotherapy of tuberculosis was based on a comprehensive and astute understanding of the physiologic chemistry of the tubercle bacillus. Unfortunately, such was not the case. Instead our approach was similar to that of countless others: a formula consisting largely of enthusiasm, hope, faith, persistence, and luck. Perhaps the latter was the most important ingredient.

The writer then adds a thought that is familiar to leprosy workers, namely, that although modern chemotherapy has done much, the final conquest of tuberculosis is not yet in sight. "Furthermore, there exist valid doubts whether the disease can ever be banished by the use of specific chemotherapeutic substances alone, even by drugs far more potent than any presently foreseeable."

In the meantime, clinical work in the chemotherapy of leprosy will continue in the main to be empirical, following in the footsteps of equally empirical phthisiologists, and will continue to be wasteful and largely unsatisfactory, until and unless the modern bacteriologist is given full opportunities to carry on studies designed to lead to directives for effective therapeusis. —H. W. W.