CORRESPONDENCE

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EXPERIMENTAL EVIDENCE FOR THE EXISTENCE OF SULFONE-RESISTANT STRAINS OF *Mycobacterium leprae*

To the Editor:

In a recent issue of The Journal (**32** (1964) 207) Dr. George L. Fite was asked to comment on the proposition: "How can it be said that, when the patient becomes unresponsive to treatment, it is because the *bacilli* have become sulfone-resistant? May it not be that the body, the tissues, have become incapable of metabolizing the drug to a form that can act on the bacilli?" His answer was that while in other bacterial infections bacteriologic methods were available for demonstrating the existence of drug-resistant mutants in patients failing to respond to treatment, in leprosy such an explanation must at present remain speculative since *M. leprae* is not cultivable and therefore cannot be submitted to bacteriologic investigation.

In a comment to this reply Dr. H. W. Wade pointed out that in the case of *M. lepraemurium*, which is also a noncultivable bacillus, it can be readily transmitted to animals and the experimental infections can be used to study the organism *in vivo*. Using these methods Hart, Rees and Valentine (*J. Path. & Bact.* **84** (1962) 105-111) clearly demonstrated that, although *M. lepraemurium* is at first responsive to treatment in mice with isoniazid, it soon acquires resistance to that drug, since bacilli recovered from the treated animals and used to infect further animals fail to respond to treatment with isoniazid. These studies clearly show that even with a noncultivable organism like *M. lepraemurium* bacteriologic investigations can be undertaken, including the development of drug resistance, as long as the causative organism can be transmitted to experimental animals. Although *M. leprae* can still not be cultivated *in vitro*, it is now fully accepted that it can be transmitted to animals using the mouse foot pad technic (Shepard, *American J. Hyg.* **71** (1960) 147-157; Rees, *British J. Exper. Path.* **45** (1964) 207-218), and therefore this infection could be used to determine the presence of sulfone-resistant strains of human leprosy bacilli.

We would, therefore, not agree with Dr. Fite that the existence of sulfone-resistant strains of *M. leprae* cannot be adequately investigated. In a recent publication (Pettit and Rees, *Lancet* **2** (1964) 673-674) we have studied experimentally and clinically seven leprosy patients who, despite 13 to 15 years of sulfone treatment still presented with active infection. Bacilli from these seven patients were used to infect sulfone-treated and untreated groups of mice and at the same time the seven patients were admitted to our Research Wards and put on high doses of sulfone by intramuscular injection. At the completion of

six months of treatment there was clinical and bacteriologic evidence of improvement in four patients and no improvement in three. In the experimental studies in the mouse foot pad the bacilli from four patients were completely inhibited by sulfones and in three patients the infection was not affected by sulfones. The three strains of bacilli which were not inhibited by sulfones in the mouse foot pad corresponded with the three patients who did not respond clinically or bacteriologically. Using the new technic for producing leprosy in the mouse foot pad, it has been possible, for the first time, to establish that sulfone-resistant strains of *M. leprae* can exist in man.

Our main purpose in replying to Dr. Fite's letter is to stress that the successful transmission of human leprosy in the mouse foot pad achieved by Shepard provides an experimental infection which can be applied to investigate many of the unsolved problems in leprosy. Our own studies show clearly the successful use of this experimental infection for demonstrating the existence of sulfone-resistant strains of *M. leprae*.

National Institute for Medical Research R. J. W. Rees, F.C. Path.
Mill Hill, London, N.W. 7
England

Research Unit J. H. S. Pettit, M.D.
Sungei Buloh Leprosarium
Sungei Buloh, Selangor, Malaysia
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