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Story Behind the Clinical Trial of B.663 in Leprosy

To THE EDITOR:

Recently noteworthy antileprosy activity of B.663, a rimino-compound of Dr. V. C. Barry’s phenazine series, has been noted by investigators at several leprosaria, e.g., East Nigeria (*), Malaysia (***) and Carville, La. (**), and at the Clinical Center, National Institutes of Health, Bethesda, Md. (**). Because of current wide interest in B.663, I thought a short history of clinical trials of the drug, with emphasis on studies of murine leprosy, would be interesting.

I have been involved in studies of the effect of Barry’s phenazine compounds on murine leprosy since 1952. In 1955 an early compound, B.283 (**), showed little activity in murine leprosy. More interest was aroused when Barry and associates reported a new, more potent compound, B.663, in 1957 (**). Commencing in September 1958, Dr. Barry supplied me continuously with small quantities of the drug. Studies of the activity of B.663 were made in mice, first with 3-week and 3-month tests, then with a long-term experiment (516 days), and finally with an established infection of murine leprosy. Among many drugs studied in this laboratory, B.663 was the only one that held murine leprosy in check for as long as 516 days, without apparent development of resistance to the drug. Furthermore, our experience showed that development of resistance of M. lepraemurium to isoniazid was markedly delayed when the animals were treated with both B.663 and isoniazid. In
various combined therapies with antituberculous drugs, significant reduction of established murine leprosy was observed only in combinations that contained a nucleus of B.663 and isoniazid (12, 13).

Although clinical trial of B.663 in pulmonary tuberculosis had been unsuccessful both in Paris and Bostel (Germany) at that time (7), with the high antimurine-leprosy activity of B.663 in mind, Dr. Barry, with the cooperation of Dr. H. G. Cochrane, arranged a pilot trial of the drug in leprosy in East Nigeria. Definite clinical and bacterial improvement was observed by Dr. S. G. Browne in lepromatous leprosy over a period of 12 months. However, a sudden increase in the bacterial index and a reappearance of morphologically normal bacilli (solid form) at the end of a one-year trial suggested that resistance to B.663 had developed in the organisms (8, 9, 18).

Being aware of the findings in murine leprosy, Dr. V. Knight of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, wished to make a thorough trial of B.663 before it was rejected prematurely. Difficulty was met in seeking a supply of B.663, since Geigy, the manufacturer, was not planning to offer a further supply of an expensive, resistance-producing drug, and a third party was not ready to take over the drug on which Geigy had the patent. Dr. Knight then wrote to Geigy in May 1962 as follows: "It occurred to me that you might like to visit here and see our new program in leprosy research and to view firsthand some of the results of Dr. Y. T. Chang in rat leprosy. B.663 is very impressive in this setting. My particular interest is that . . . resistance to the drug may not develop." In response to this letter, Dr. W. Vischer, Chief, Department of Bacteriology, Geigy, Basel, visited my laboratory in September 1962, and later brought my results to the attention of his company. Subsequently, a sufficient amount of B.663 was supplied by Geigy for clinical trial at the National Institutes of Health.

The suppressive activity of B.663 in leprosy, observed by Dr. Browne, was confirmed by Dr. Knight and his associates. There was no appearance of resistance to B.663 after continued administration of the drug for as long as 3 years (19). Furthermore, Dr. Knight and his associates (1, 10) and Dr. Browne (2, 7) also observed that B.663 exhibited a definite suppressive action on the occurrence of erythema nodosum leprosum (ENL) in leprosy.

Clinical trials performed in other leprosaria, e.g., at Kuala Lumpur, Malaysia, and Carville, La., have shown no appearance of resistance of M. leprae to B.663 (11, 13). Dr. Browne, in an appraisal after a three-year trial, concluded that the resistance he had observed in the first group of patients after 12 months' treatment was a "transient phenomenon" (8). Apparently the reappearance of the solid form of bacilli in Browne's patients at the end of 12 months has to be interpreted in some other way than simply as a revival of multiplication by previously suppressed organisms. This, in turn, may throw some doubt on the hypothesis proposed by Fees and Valentine in 1962 that solid bacilli are viable and irregularly stained bacilli dead (12). Other experiments, especially those of Shepard (16, 17), emphasize the uncertainty. A standard method for counting solid and nonsolid acid-fast bacilli is essential in solution of the problem.

Murine leprosy represents an infection with progressive multiplication of M. leprae, which eventually becomes systemic. The growth characteristics of the etiologic agent are similar to those of M. leprae in lepromatous leprosy. Eradication of the infection requires agents with prolonged antimicrobial activity without the development of resistance of organisms to the drugs. For studies of this type of infection, murine leprosy offers a suitable infection. The advantage of the murine leprosy model for screening new potent drugs in the treatment of leprosy is clearly shown in the case of B.663. Had Dr. Knight and the Geigy representatives not been convinced by the findings of murine leprosy studies, B.663 might still be considered a useless, resistance-producing substance, discarded for want of a thorough clinical trial.

Thus, two conclusions may be drawn...
from the B.663 trial. First, the murine leprosy model has offered a valuable tool for searching and evaluating new potent drugs for the treatment of leprosy. Second, the solid appearance of M. leprae is not necessarily an indication of the viability of the bacilli.

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To the Editor:

The first part of the letter from Dr. Dharmendra (The Journal 34 (1966) 192-193) on our paper "Epidemiology of disability in leprosy--Part 2" carries matter that we consider irrelevant, but in the later part he raises certain questions that we would like to answer.

(1) As to the inclusion of anesthesia as disability, careful reading of our paper will show that only extensive anesthesia over the hands was taken as disability, which undoubtedly it is. (2) Objections to the use of data collected by paramedical workers do not appear to us to be valid, particularly as, in this case, the paramedical worker was experienced and reliable, and received constant guidance from us. It may be noted that although he took issue with us for using data collected by a paramedical worker, Dr. Dharmendra based some of his own arguments on data collected by paramedical workers. (3) The reference to Dr. Wardekar's work appears to us to be aside from the main point and inexact as respects prevalence and incidence. Dr. Wardekar's work refers to detection and treatment of early cases, whereas ours does not. His paper reports on the prevalence rates of deformity as found in certain surveys, and also on the incidence rates of deformity in certain groups of patients followed up for two to six years. To prove his contention, Dr. Dharmendra compares one of the prevalence rates (24%) with one of the incidence rates (6%), while Dr. Wardekar himself has rightly refrained from doing so. To us such a comparison does not appear permissible.

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24 November 1966