Medical Memoranda

Dapsone-resistant Lepromatous Leprosy in England

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Since the discovery by Shepard (1960) that limited multiplication of *Mycobacterium leprae* occurs in the pad of the mouse foot the technique has been used to test anti-leprosy drugs in experimental animals (Shepard and Chang, 1962, 1964; Pattyn and Royackers, 1965; Rees, 1965), and also to confirm cases of presumed dapsone resistance in Malaysia (Pettit and Rees, 1964). Therefore, when a lepromatous patient under the care of one of us (A. R. D. A.) began to deteriorate despite treatment, similar investigations were undertaken, and we present an account of the first proved case of dapsone-resistant leprosy in England.

CASE HISTORY

The patient, a 33-year-old Anglo-Indian from Bengal, was first seen at the Liverpool School of Tropical Medicine in July 1961. He stated that he was well on arrival in England in 1958, but since November 1960 he had developed numerous red patches and, subsequently, painless lumps on his skin. He denied ever having had leprosy.

Examination revealed typical appearances of lepromatous leprosy; skin smears contained very numerous acid-fast bacilli, and the lepromin test was negative. He was admitted to Sefton General Hospital for treatment with dapsone, the maintenance dose being 100 mg. daily, and with thiambutosine, 2 g. daily. He responded well, so that by June 1963 most of the lesions had faded and the skin smears contained markedly fewer acid-fast bacilli, which were all fragmented. The thiambutosine was stopped, and he was discharged from hospital on dapsone 100 mg. daily.

He remained well for nine months, but then began to develop tiny lumps on his limbs and subsequently also on his body. Examination in October 1964 confirmed the presence of scattered, reddened, and sometimes scabbed nodules, 3 to 8 mm. in diameter, on the face, limbs, chest, and buttocks, with lepromatous infiltration of the skin. However, in contrast to these signs of active progressive leprosy, the skin of the ear lobes and adjacent face was lax and wrinkled. In addition, there was glove-and-stockings anaesthesia, with slight nerve-thickening, and the testes were hypotrophic.

Slit-skin smears were made from both ear lobes and from representative nodules. The bacterial index (density of acid-fast bacilli) estimated by Ridley's (1958) method averaged for the ears 3.5 and for the nodules 5.0; the morphological index—percentage of solid-staining presumed viable bacilli (Waters and Rees, 1962)—was 5 and 67 respectively. A biopsy specimen of a nodule was taken; part of the material was used for experimental studies and histological examination of the remainder revealed active lepromatous leprosy.

It was thought that the relapse was due either to the development of drug resistance at a hitherto unreported early stage of treatment, or to the patient's failure to take dapsone since leaving hospital. Random serum and urine sulphone levels were both extremely low, suggesting irregular treatment. It was decided to investigate, for a limited period, the effect of intramuscular dapsone at the very high dose of 600 mg. twice weekly. However, clinically he continued to deteriorate rapidly. Therefore in March 1965 he was admitted to the Jordan Hospital, Redhill, where repeat skin-smear and histological examinations confirmed the failure to respond to parenteral

therapy. Furthermore, it was discovered that he had in fact received sulphone treatment some 15 years previously in an Indian leprosarium.

EXPERIMENTAL STUDIES

With the use of techniques described by Pettit and Rees (1964), a suspension of *Myco. leprae* was prepared from the biopsy material and used to inoculate 36 mice with approximately 10,000 bacilli in the pad of each hind foot. The animals were then divided into six groups; one acted as untreated controls, the other five each received one of the following drugs mixed in their diet: 0.1% dapsone, 0.025% dapsone, 0.1% thiambutosine, 0.2% thiacetazone, and 0.1% sulphadimethoxine. The mice were killed after five to nine months. Classical limited multiplication of *Myco. leprae* were detected in the pad of the foot not only of the control animals but also of the dapsone-fed animals, whereas the infection was completely suppressed by thiambutosine and thiacetazone, but only partially suppressed by sulphadimethoxine.

COMMENT

Dapsone-resistant leprosy is rare. Moreover, the three patients of Pettit and Rees (1964) had all received sulphones for many years, as also, despite his stated history, had our own patient.

The application of the mouse-foot-pad test not only confirmed our clinical diagnosis of drug resistance but also provided guidance for the patients' future management. Although Hirako and Sakurai (1963) have suggested that long-acting sulphonamides may be of value in sulphone resistance, we were not surprised to find that partial cross-resistance had occurred with sulphadimethoxine, as the sulphones and sulphonamides are chemically so closely related. However, resistance to thiambutosine had not developed, and the patient has responded well to a further course of this drug, combined with Vadrine (an oxydiazoline compound), and subsequently with thiacetazone.

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