

Proven Primary Dapsone Resistance in Leprosy—A Case Report

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A patient is described who at the age of 10 years developed tuberculoid leprosy; during the next 2 years while on oral dapsone therapy, his condition deteriorated and he became lepromatous. Both clinically, and experimentally by drug sensitivity testing in mice, his strain of *Mycobacterium leprae* was found to be fully resistant to dapsone. His father was a known case of secondary (acquired) dapsone resistance. The potential medical and economic importance of primary sulphone resistance is discussed.

Introduction

Clinical and experimental proof of secondary dapsone resistance (DR) in lepromatous leprosy was first obtained in 1964 by Pettit and Rees, more than 20 years after the introduction of the sulphone drugs. In their definitive account, Pettit *et al.* (1966) predicted that sooner or later primary cases of sulphone resistance would arise. Despite this warning, there is an apparent lack of anticipation of the condition. Therefore we now report our first proven primary-resistant patient, the son of one of the original resistant cases.

Case Report

The patient, ZA, was born in 1964. Both his parents were receiving treatment for lepromatous leprosy. His father (case number 9 of Pettit *et al.*, 1966) had been admitted to Sungei Buloh Leprosarium in 1950, but by 1964 he had relapsed with active leprosy. As his strain of *Mycobacterium leprae* was found to be sensitive to 0.025% dapsone in the mouse diet (but was not tested against lower concentrations of drug), and as he showed initial clinical improvement on dapsone 300 mg twice weekly by injection, he was reported as not suffering from DR. However, after a year he began slowly once again to relapse; his strain of *M. leprae* obtained in 1968 was shown to be resistant to 0.01% dapsone in the mouse diet (equivalent to a dosage of 100 mg dapsone daily in a full-sized adult); and his treatment was changed to clofazimine in May, 1969.

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His son, ZA, presented in 1970, with 2 hypopigmented macules. A diagnosis of indeterminate leprosy was tentatively made; however, no treatment was given, but the patient was placed under observation. In May 1974, he was found to have developed an anaesthetic, hypopigmented patch on his back, and the left great auricular nerve was thickened. Tuberculoid leprosy was diagnosed, and treatment was commenced with dapsons 100 mg twice weekly by mouth. His supply of dapsons was collected regularly every 3 months. However, in September 1975, his lesions became red and swollen, new lesions appeared and the left ulnar nerve was noticed to be enlarged and tender. A "reversal" or "upgrading" reaction, due to increase in cell-mediated immunity under effective treatment (Ridley, 1969; Waters *et al.*, 1971), was diagnosed, and treated with a short course of prednisolone. The reaction recurred in June, 1976; treatment with prednisolone was recommenced and he was admitted to the leprosarium, where the dosage was increased to 200 mg twice weekly and given by injection.

When first seen in the Leprosy Research Unit, in July 1976, ZA was clinically suffering from active borderline-lepromatous (BL) (Ridley and Jopling, 1966) leprosy in mild reaction, with multiple vague hypopigmented macules, erythematous moist plaques and papules, and widespread moderate nerve enlargement with some nerve tenderness. Slit skin-smears gave an average bacterial index of 3.7, and a morphological index of 2. Skin and superficial radial nerve were biopsied; histological examination of the skin revealed active sub-polar lepromatous leprosy (LLs) (Ridley, 1974), with minimal reaction (Dr D. S. Ridley) and that of the nerve showed early lepromatous leprosy developing from borderline leprosy (Dr A. C. McDougall).

As, over the course of 2 years, ZA had "downgraded" from presumed borderline-tuberculoid (BT) to lepromatous (BL/LLs) leprosy, it was considered that either he had failed to take the prescribed dapsons, or else he had suffered from the first from (primary) DR. Treatment was continued for 3.5 months with dapsons twice weekly by intramuscular injection but without any therapeutic response. His skin lesions remained active, and neuritis, especially of the left median and ulnar nerves, persisted. Nerve function began to deteriorate. Therefore treatment was changed in October to rifampicin and clofazimine. Rapid clinical improvement ensued, although the neuritis temporarily relapsed due to a reversal reaction. After 6 months on this alternative, effective treatment the skin lesions were all inactive. The skin was once again biopsied, and histological examination revealed quiescent mainly BT leprosy (but with some lepromatous foci), acid-fast bacilli were present in nerves only, and it was considered that marked upgrading towards tuberculoid leprosy had occurred (Dr D. S. Ridley).

Experimental Methods and Results

M. leprae obtained from a fresh tissue skin biopsy in July 1976, and inoculated into mouse footpads (Rees, 1967), multiplied in mice receiving 0.01% dapsons in their diet.

An aliquot of the superficial radial nerve, biopsied in August 1976, was sent

as fresh tissue on wet ice to the National Institute for Medical Research, where a suspension of *M. leprae* was prepared from it, and inoculated into mouse footpads. This strain was also found to be fully resistant to 0.01% dapsone in the mouse diet.

Discussion

The history of our patient is a salutary warning to all engaged in leprosy control schemes. Although secondary dapsone resistance (DR) has only been reported in lepromatous (LL and BL) leprosy (Pearson *et al.*, 1975), it was anticipated that primary resistance would occur in any type of leprosy, with grave economic implications for developing countries (WHO 5th Expert Committee on Leprosy, 1977).

Our patient was suspected of suffering from indeterminate leprosy at the age of 6 years. Four years later, tuberculoid leprosy was diagnosed, and dapsone therapy was commenced. It is academic to argue whether or not he took his treatment regularly or at all, as either way the evidence confirms primary drug resistance. Relapse due to the development of secondary DR has not been detected in Malaysia in less than 5 years of treatment (Pearson *et al.*, 1975) and in all cases there was an initial response to therapy. This is in marked contrast to ZA. The whole progression of his disease, throughout his 2.4 years on dapsone, is in keeping with that of a patient receiving no effective treatment, with the development and spread of new skin lesions, the increasing involvement of the nerves of predilection, and the loss of cell-mediated immunity associated with a shift from BT to LLs leprosy. Therefore he underwent a mild "downgrading", not a "reversal" reaction. We have observed a similar downgrading from borderline to LLs leprosy in a patient undergoing investigation for secondary thiambutosine resistance (Pearson and Waters, unpublished data).

DR was proved, first clinically by his failure to respond while receiving 3.5 months of parenteral sulphone therapy in hospital, and then experimentally by dapsone-sensitivity studies in mice of his strain of *M. leprae* obtained from both skin and nerve (performed in Malaysia and London respectively). Both tests showed that his strain was fully resistant to dapsone, at the same level as the strain obtained from his father in 1968. During the first 5 years of his life, there was ample opportunity for ZA to become infected with the latter strain of *M. leprae*, as it was not until 1969 that his father's treatment was changed.

Primary DR is now a very real risk wherever secondary DR has occurred. *Prime facie* evidence of primary resistance has been reported from Columbia (Londono, 1977), and from Micronesia, where 2 child contacts of a known resistant patient developed tuberculoid leprosy (Russell *et al.*, 1976). Pearson *et al.* (1977b), in the first organized survey for primary DR, found that 5 of 8 strains of *M. leprae* from newly diagnosed cases of lepromatous leprosy in Addis Ababa, where there is a very high incidence of secondary DR (Pearson *et al.*, 1977a) were resistant to dapsone; although the levels of drug sensitivity were not fully titrated at least 2 strains were resistant to 0.001% dapsone in the mouse diet. Jacobson (1977) has also briefly reported the detection of 4 cases of primary DR, at the 0.0001% (but sensitive at the 0.001%) level in the diet of

the mouse. As usual, prevention is to be preferred to cure; this in turn implies the full-scale application of those measures recommended by the WHO 5th Expert Committee on Leprosy (1977) designed to keep the incidence of secondary DR to a minimum, and to recognize it early and to treat it effectively whenever it occurs.

Our patient is important, not because he is perhaps the first case of primary DR to be both clinically and experimentally proven, but rather because his history illustrates the risks associated with unrecognized primary resistance occurring in tuberculoid leprosy. There is a great need for an increased awareness of the condition. This will involve better training of both doctors and para-medical workers involved in leprosy control schemes. It also implies better communication between those treating diagnosed cases of DR and those involved in the tracing and supervision of contacts, although the majority of primary DR patients may well have no history of household or familial leprosy.

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