

DRUG RESISTANT LEPROSY -- A COMPARISON BETWEEN PROVEN DAPSONE
AND PROVEN THIAMBUTOSINE RESISTANCE

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We have recently analyzed the first 100 consecutive proven cases of sulfone resistance in leprosy, detected in Malaysia between 1963 and 1974. Proof of resistance was clinical in 82 patients, and by drug sensitivity testing in mice in 98 patients; 80 patients were proved both clinically and experimentally and there was no discrepancy between the two methods. Clinical evidence of relapse due to the development of drug resistance occurred 5 to 24 (average 15.8) years after commencing sulfone treatment. Where records were available, more than two thirds of the patients became smear negative for a period before relapsing. Low dosage favored the appearance of sulfone resistance. All patients gave a history of having responded to sulfone treatment for many years before relapsing. The striking clinical feature was the simultaneous presence of new, active, usually asymmetrical lesions, together with evidence of old, treated leprosy. Bacteriologically, a patient's individual smears often showed marked variation between different sites. Histologically, all patients were "lepromatous", 87 being classified as LL or LI and 13 as BL. Twenty-five showed histoid, expansile or hyperactive features.

Although thiambutosine was the drug of second choice for a decade from 1958, it was seldom prescribed in Sungei Buloh Leprosarium and to date only 14 proven cases of thiambutosine resistance have been detected. Clinical proof was obtained in 12 patients, 4 of whom received carefully supervised oral thiambutosine (1 g twice or thrice daily) as inpatients, and 8 who were treated with parenteral thiambutosine 1 g once weekly. Experimental proof was obtained by feeding mice inoculated with *Mycobacterium leprae* with 0.1% thiambutosine in their diet. Eleven strains (including 2 from patients who could not be tested clinically) multiplied in the thiambutosine fed mice; and the result from one strain is still awaited. However, in marked contrast to our experience with sulfone resistance, 2 strains from patients clinically resistant to oral thiambutosine were found to be sensitive to thiambutosine in mice; the one of these 2 patients who has been investigated has been found to be a very poor absorber of thiambutosine (Ellard, personal communication). A second contrast with sulfone resistance is the relatively brief "incubation period" of thiambutosine resistance, clinical evidence of which developed 16 months to 11 years (average 5.2 years) after commencing treatment. Indeed, the 4 lepromatous (LL or LI) patients given thiambutosine for active DDS-resistant leprosy

averaged only 2.8 years, and the 9 patients treated with thiambutosine because of sulfone allergy, some of whom were nonlepromatous at first diagnosis, averaged 6.7 years. The clinical picture of thiambutosine resistance was not as clear cut as in DDS resistance. Only patients who did not suffer from LL or LI leprosy on first diagnosis became smear negative before relapsing; lepromatous patients who relapsed were usually clinically indistinguishable from previously untreated disease; the first clinical sign of relapse in 3 patients who were thought to have suffered originally from BB or BL leprosy was the development of asymmetrical borderline-type annular lesions.

The significance of these findings will be discussed.