

DISCUSSION AND CONCLUSIONS

At the time that the THELEP programme began, the two major concerns of the scientists working in the area of chemotherapy were the phenomena of microbial persistence and drug-resistance. It appeared certain that relapse caused by the emergence of drug-resistant *Mycobacterium leprae* could be prevented by employing combined (multidrug) therapy, particularly combinations including rifampicin, which was known to exert a powerfully bactericidal action against the organism. It was also clear that control of leprosy by chemotherapy would be possible only if chemotherapy of finite duration were curative; long experience with dapsone as monotherapy had demonstrated that neither patients nor the treatment services could be expected to comply with treatment of indefinitely long duration. However, rifampicin as monotherapy had recently been shown to be incapable of eradicating *M. leprae*. And it was feared that persistence of viable organisms in the lepromatous patient, whose immune response to the organism was known to be deficient, would lead inevitably to relapse after cessation of the chemotherapy. Workers hoped that a multidrug regimen could be discovered that was curative -- *i.e.*, capable of eradicating persisting *M. leprae*, thereby preventing relapse.

As its first priority, therefore, the THELEP Scientific Working Group undertook to conduct comparative trials of multidrug regimens, employing measurements of the proportion of persisting *M. leprae* as the index of efficacy. Trials of regimens of varying intensity, all including rifampicin, were mounted in Bamako, Mali, and in Chingleput, South India, involving finally a total of 215 patients with multibacillary leprosy, who were believed to have had no previous treatment. Persisting *M. leprae* were detected in 43 (7.8 per cent) skin-biopsy specimens among a total of 554 specimens obtained at intervals of 3, 12 and 24 months from 38 of a total of 203 patients during treatment with five combined drug regimens. The proportion of specimens in which persisting organisms were discovered could not be shown to vary with regimen or duration of treatment. The regimen consisting of a single large initial dose of rifampicin plus daily dapsone was not shown to be less effective, in terms of the proportion of specimens in which persisters were detected, than regimens consisting of rifampicin, dapsone and clofazimine or protionamide, each drug administered daily. The average patient's burden of persisting *M. leprae* was calculated to lie in the range 50 000 - 250 000 at each of the intervals, numbers of organisms much smaller than those that had been anticipated. These data were consistent with information regarding the relatively small risk of relapse after cessation of chemotherapy among patients with multibacillary leprosy, information that was not available when the clinical trials were mounted. In addition, the small numbers of persisting *M. leprae*, which appear to reflect the role of rifampicin as a component of the drug-combination, provided strong support to the multidrug regimen recommended for treatment of multibacillary leprosy by the World Health Organization Study Group on Chemotherapy of Leprosy for Control Programmes.

An important by-product of these trials were the data on primary resistance to dapsone. Approximately 37 per cent of the 131 patients with lepromatous leprosy admitted into the THELEP controlled clinical trials in Bamako and Chingleput, whose *Mycobacterium leprae* obtained from pretreatment biopsy-specimens could be tested in mice, were found to harbour dapsone-resistant organisms, and were presumed to represent instances of primary resistance to dapsone. Although the majority of these patients harboured strains of a low degree of resistance, 20 per cent harboured organisms of an intermediate degree of resistance. These