Considerations on the Treatment of Leprosy

TO THE EDITOR:

In considering the Fifth Report of the WHO Expert Committee on Leprosy (Technical Report Series, 607, Geneva, April 1977); the Heathrow Report (ILEP No. 1, London, August 1977); and the Workshops on Experimental Chemotherapy and Epidemiology, Control and Field Therapy of the XI International Leprosy Congress (November 1978, Mexico), the following observations appear warranted:

1. For the treatment of lepromatous leprosy and for the prevention or treatment of dapsone resistance, 9 drugs are recommended in the above documents.

These drugs may be classified into four groups fundamentally:
a) Drugs with clinically demonstrated, known therapeutic activity in leprosy:
dapsone (oral or by injection)
clofazimine
rifampin
b) Drugs which have been used clinically in the past but which, more recently, have been discontinued because of low therapeutic activity or for toxicity. The value of these drugs is still under investigation:
thiambutosine (Ciba, 1906)
thiacetazone (TB1/698)
sulfamethoxypyridazine
c) A drug which is used clinically, but with doubts about its efficacy:
acedapsone (DADDS)
d) Drugs which have had essentially no controlled clinical trials in leprosy and which are still under assessment:
ethionamide
prothionamide

2. With one or more of the nine drugs mentioned, 11 regimens for the treatment of lepromatous leprosy are recommended, namely:
dapsone alone
rifampin and dapsone (2)
clofazimine and dapsone
ethionamide and dapsone
thiacetazone and dapsone
dapsone by mouth and injection
rifampin and clofazimine
ethionamide and clofazimine (2)
rifampin and ethionamide

With the majority of these regimens there is no therapeutic experience clinically, and the recommendations have been made based either on data obtained in the footpad model of *M. leprae* infection in intact mice or on theoretical considerations.

3. More recent experience with all these regimens has frequently emphasized monitoring the response of treated patients by serial inoculations of bacilli from patients into normal mice. In this regard, it should be pointed out that:
a) Over twenty years was needed to study the anti-leprotic activity of dapsone, and until a few years ago, the proper dosage(5 to 10 mg or 50 to 100 mg daily) was not known. The anti-leprotic activity of clofazimine and rifampin was established after almost ten years of clinical experience. It should be added that during this period little was known about dapsone resistance and drug-sensitive survivors ("persisters").
b) If it took several decades to establish the anti-leprotic activity of dapsone, clofazimine and rifampin, how many decades will it take to know the anti-leprotic activity of 11 different regimens, using 9 drugs, in previously treated patients, considering the additional problems of drug resistance, "persisters," etc.?

4. Strong emphasis has been placed on the model of *M. leprae* infections in the footpads of normal mice in almost all of the more recent experimental and clinical trials dealing with the chemotherapy of leprosy. Bechelli and Guinto [1] have raised fundamental objections to the use of results obtained with this model to make implications for the clinical therapy, epidemiology and control of leprosy. The following points are taken from this work.
a) "It is considered premature to apply laboratory findings to human leprosy before clinical and epidemiological studies have been made in man."
b) "*M. leprae* 'infections' in the footpads of mice, limited at best, die off after reaching a certain level, indicating that mice and human are not alike in their susceptibility."
c) "Judged by their great effectiveness in leprosy in mice, these two measures together—dapsone and B.C.G. vaccination—should by now have accomplished a world-wide reduction in the prevalence of leprosy but there is not evidence that such a reduction has taken place."
d) "It is unquestionably extremely hazardous to extend the results in the mouse to man." (Levy)
e) "It should be appreciated that even the most irregularly-treated of these patients would be considered as grossly over-treated on the basis of the laboratory findings in mice."

If the fundamental validity of the model of *M. leprae* infections in the footpads of normal mice is questioned, then the fundamental validity of many of the assumptions made in the more recent recommendations for the treatment of leprosy may be questioned. Indeed, if the view is taken that the mouse footpad model is completely lacking in validity, then many of the more recently recommended treatment regimens may also completely lack validity. If there is indeed no suitable model to test new antileprosy drugs in animals or *in vitro*, then the many drugs, the many regimens, the revival of old and ineffective drugs, etc., could be interpreted as being completely disorderly, confused and likely to be ineffective. Taken further, this line of reasoning could lead to the conclusion that leprosy control by chemotherapy is unattainable and that it is impossible to predict the future course of leprosy in the world.

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REFERENCE

1. Bechelli, L. M. and Guinto, R. S. Some recent findings on *Mycobacterium leprae*. Implications for the therapy, epidemiology and control of leprosy. Bull. WHO **43** (1970) 559–569.