Sulfone Resistance and Leprosy Control

The emergence of sulfone-resistance is bringing a complete reappraisal of leprosy therapy. Several meetings and reports have recently emphasized the need for strictly controlled high dosages of sulfones and in certain cases combined chemotherapy. The WHO Leprosy Expert Committee on Leprosy (1976) has issued precise recommendations which can be summarized as follows:

1. In order to prevent the emergence of secondary sulfone resistance, the treatment of newly diagnosed cases should be based on dapsone commenced, maintained and continued regularly in full dosage and without interruption irrespective of lepra reaction.

2. Initial combined therapy with sulfones and second-line drugs should be given to lepromatous (LL) and borderline (BL, BB) cases.

3. Combined therapy with second-line drugs should be used for cases with confirmed or suspected dapsone resistance.

These recommendations have been amplified and detailed at recent workshops held in Manila (1977) and Jakarta (1977) at the initiative of the Sasakawa Memorial Health Foundation, and at the joint meeting of ILEP (International Federation of Anti-Leprosy Associations) Medical Commission and LEPRA Advisory Board in Heathrow (1977).

The basic problem however is that there is much more in sulfone resistance than a simple problem of therapy. The emergence of resistance obliges us to reconsider drastically our strategy of leprosy control. The issue is not to find the best regimen to suit individual patients in hospitals, it is to design the best strategy to prevent resistance when treating large numbers of patients, that is patients by the thousands or the hundreds of thousands.

There is no doubt that sulfone regimens as applied for the last 20 years, and especially during the last 10 years, have been largely based on convenience. Leprosy treatment had to be cheap, it had to be administered unsupervised by auxiliary workers, it had to be delivered in far away villages, it had to be free of toxicity and undesirable reactions. All this was quite consistent with the need of treating millions of patients in countries with poor health resources, insufficient manpower and limited facilities. The sulfones remarkably fulfill these conditions. Mass treatment of ambulatory patients could thus be organized. In a number of countries it was responsible not only for the cure or at least considerable improvement of many patients, but also for a marked decline of incidence. Where no dispensaries existed and local conditions precluded the deployment of mobile teams, self-medication was instituted. Patients traveled days and weeks to get their monthly or quarterly supply of dapsone.

Convenience however was the *leitmotiv*. From a fortunate logistic context it tended to transform into a myth to which leprosy had to adhere. Since very high dosages administered at the beginning of the sulfone era were in all likelihood associated in leprosy patients with a high incidence of lepra reaction and other complications such as dermatitis and psychosis, lower doses were recommended, which relaxed the requirements for

medical supervision and lifted the possible need for facilities to hospitalize reactional patients. Closely watched administration of the drug was extended to distribution of tablets by untrained laymen and further to uncontrolled remittance of supplies for self-medication. Unsurprisingly, in some countries sulfones were sold in markets and all over the place for all kinds of ailments. This was not considered so bad for after all some of the drug reaches the patients any way so why not consider the amount of drug imported to a country as an indicator of control effectiveness. When supply lines broke down following the decision of international agencies to cut their support for leprosy control, existing stocks were at times stretched to the maximum in order to keep under treatment the largest possible number of patients for as long as possible, with the result that minimal dosages were administered.

Nature, through the usual mechanism of evolution, was of course the major culprit. The probability of resistant strains emerging increases with the number of patients treated, the length of treatment, the irregularity of intake, and inversely with dosage. As though nature needed to be assisted, experts advocated in the late 1960's that dosages be reduced, a recommendation for which no rationale can be found and whose result could only be to speed up the emergence of resistance. As a consequence, thousands of lepromatous patients have now been found who suffer from secondary resistance and can no longer improve with dapsone. New patients with primary resistance are reported. Many more patients are in some way incubating resistance, that is the population of resistant bacilli in their organisms has not yet reached the level where clinical resistance becomes manifest but that should not wait for long. In other words, another disease is replacing leprosy caused by *M. leprae,* and for this disease there is no easy cure. Drugs do exist. There are at the moment at least clofazimine and also rifampicin, the only known bactericidal drugs in leprosy. But for these drugs, time allocated is limited before resistance will appear and no failures are permitted. Double or quits.

Again, it is not just a problem of medicaments. A completely new strategy is needed. It would be the worst mistake to think that by providing rifampicin by the megatons to governments or agencies we will solve the problem. Leprosy control must be viewed as a system in which every component is dependent on and has influence on the others. Resistance and its management have wide and far-fetching implications. Chemotherapy cannot be viewed in a vacuum. It is a tool for control. The long-term purpose of combined therapy is not only to cure the patient more effectively and faster, it is primarily to interrupt transmission, that is to dry up the reservoir of multibacillary patients as a source of infection. The effectiveness of chemotherapy from an epidemiologic viewpoint and its relevance as far as populations are concerned, depends on to whom it is administered. This requires that the target group needing combined or substitute chemotherapy be perfectly defined: the long-treated cases with resistant bacilli (secondary resistance); the long-treated cases which, due to inappropriate treatment, could sooner or later develop resistance (incubating secondary resistance); the new cases infected with resistant bacilli (primary resistance); or even all new cases.

The short-term and long-term effectiveness of resistance control will depend on which of those groups are taken into consideration. It will also determine the costs, since the respective sizes of these different populations are quite different. In many situations, for economic reasons, it will not be possible to take into consideration all four groups. A choice will have to be made with respect to the most cost-effective strategy. An additional problem rises from the fact that confirmation of resistance under field conditions is not generally possible. Resistance can only be suspected on the basis of the Bacteriologic and Morphologic Indices and *prima facie* (clinical) evidence. Practically, this implies that old cases should be closely followed up bacteriologically and clinically, in order to detect *prima facie* resistance. It requires an extension of the laboratory facilities in the field (generalization of adequate bacteriologic examinations as well as upgrading of the personnel both in clinical and laboratory skills). It also requires that convenient standard forms and models be adopted for the clinical and bacteriologic follow-up of patients over the years.

Whatever the mix of strategy selected (type of drugs and target groups), resistance

therefore has a number of implications for leprosy control. These are:

a) a strict operational control of the line of drug supply with firm commitment for continued supplies;

b) a strict supervision of treatment in lepromatous (and other infectious) patients, including random urine control for drug intake of patients in self-medication;

c) laboratory facilities in the field for the bacteriologic follow-up of patients, including performance of the Morphologic Index;

d) an appropriate clinical follow-up of patients with the possibility of linking the observations in successive years. This requires adequate forms and records;

e) facilities for the hospitalization of a larger number of patients than at present during the first few months of treatment. This will require building or remodeling of facilities, and/or appropriate arrangements for hospitalizing the patients in general hospitals;

f) the availability of thalidomide and the possibility of using this drug under appropriate conditions of safety;

g) an appropriate system of detection and referral of patients with lepra reaction;

h) a general upgrading of the auxiliary personnel in charge of leprosy control, with respect to laboratory skills, clinical expertise, handling of reactions, and health education.

The fulfillment of these conditions is required before considering the establishment of new therapeutic policies in relation to resistance.

As noted by Ishidate at the Manila meeting, chemotherapy in leprosy is becoming a highly complex and complicated task. Indeed, control of leprosy is becoming a highly complex and complicated task. To what extent this is compatible with the new and much needed approach to health based on primary health care remains to be seen.

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