WORKSHOP 3: CHEMOTHERAPY

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Participants

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Invited But Unable to Attend

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The Workshop reviewed the progress of multidrug therapy (MTD) in the context of reported side effects and relapse rates. The application of MDT has been accepted world wide over the past decade. More than 3 million leprosy patients have already received WHO and similar MDT, and many have been released from control. However, about 50% of the currently registered patients are not receiving MDT. Therefore, the greatest immediate need is to implement MDT to all registered cases.

In spite of the general acceptance of clofazimine, a drug which has the additional value of reducing the incidence of erythema nodosum leprosum (type 2) reactions, its effect of increasing skin pigmentation may result in poor compliance in certain patients and ethnic groups. The alternative, prothionamide, has some gastrointestinal side effects and a dose-related hepatotoxic effect. Other problems encountered include those of geography (so that monthly supervised drug distribution may be difficult because of the terrain), intercurrent disease, inadequate infrastructure and in paucibacillary leprosy (PBL) the difficulty of distinguishing late reversal reaction from bacteriological relapse due to treatment failure. Fortunately, rifampin resistance remains very rare although its prevention depends upon careful and correct implementation of MDT.

Relapses. It is now over 20 years since the start of the Malta trial and more than 10 years since the introduction of WHO MDT. Some information on relapse rates in multibacillary leprosy (MBL) is now available, although these are largely based on the original groups of patients, many of whom had received prior, long-duration dapsone monotherapy, so that their bacterial loads were often low. In Malta and Paraguay (using rifampin and Isoprodian) and in South India (using WHO-MDT and the similar THELEP regimen), rates have been extraordinarily low and very acceptable. The few relapses detected have occurred 5 or more years after stopping therapy. However, very recently reported studies in Africa, in which varieties of short-course regimens were given to previously untreated MBL patients, have resulted in significant relapse rates, some of which are unacceptably high. Moreover, relapse rates were significantly higher in patients with a high (5.0 or more) bacterial index (BI) compared with those with a BI of 4.0 or less. Latest results suggest that the rate is probably unacceptable in one group which received the WHO MBL regimen for a fixed duration of 2 years. Therefore, the Workshop suggested that the fixed-duration regimen may prove to be inadequate in previously untreated LL patients with a high bacterial load, and counselled caution in the widespread adoption of a 2-year, fixed-duration treatment of WHO-MDT until further data are available. It also noted that many relapses are occurring late and, therefore, 5 years' post-treatment follow up appears to be very inadequate, 8–10 years being the minimum required. In view of one claim that a period of daily rifampin has some advantages in terms of relapse rates over totally intermit-

tent rifampin, ongoing analysis of the data from long-term follow up of such regimens is needed.

PBL relapse rates have been acceptably low world wide. There is a great need for the further development of tests for distinguishing reversal reactions from bacteriological relapses.

The Workshop emphasized the need for the careful investigation of all post-MDT relapse cases, according to standard protocols.

New drugs. The Workshop welcomed the discovery and development over the last 5 years of the new antileprosy drugs. These include certain of the 4-fluoroquinolones, minocycline and clarithromycin. Mouse studies have shown them to be both bactericidal and second only to rifampin in their rates of killing *Mycobacterium leprae.* Pilot clinical trials in lepromatous leprosy have been completed and have confirmed that these new drugs are highly effective, both clinically and microbiologically. The Workshop also noted the current work on other drugs, such as fusidic acid and the combination brodimoprin plus dapsone.

There is now a need for the setting up of long-term clinical trials (in addition to the current ofloxacin trial) of a number of carefully selected regimens, noting both efficacy (judged chiefly by long-term relapse rates) and also drug interactions, toxicity, acceptability and effect (if any) on reactions.

These new drugs (ofloxacin, pefloxacin, sparfloxacin, minocycline and clarithromycin) need to be used with care and caution, and should not be given as monotherapy. In the short term, they may prove important in the treatment of patients who are intolerant to one or more of the standard drugs, or who suffer from proven drug resistances (especially to rifampin) or from intercurrent disease precluding the use of a standard drug.

The Workshop considered the possible value of chemoprophylaxis and immunoprophylaxis in areas of low and falling endemicity, but there were insufficient data on which to base recommendations.

Although the outlook for leprosy is now very hopeful because of the widespread application of MDT and the potential application of the new drugs, there is still a great need for continued long-term and careful chemotherapy work, both in leprosy control programs and in the various integrated programs.