WORKSHOP 2: CHEMOTHERAPY, CLINICAL AND EXPERIMENTAL

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The 5 years since the Delhi Congress have seen a number of important advances in the chemotherapy of leprosy. Studies have continued to demonstrate a high frequency of relapses with secondary dapsone resistance during dapsone monotherapy and a high prevalence of primary dapsone resistance, further emphasizing the need for multidrug therapy (MDT). On the other hand, primary resistance to rifampin has not yet been recognized, even in those areas in which secondary resistance to rifampin has occurred as a consequence of rifampin monotherapy. Most importantly, implementation of MDT has expanded so that, by this time, more than 2 million patients have completed MDT. MDT has been implemented in most endemic countries although, in the majority of the countries, only a proportion of patients has been covered. MDT has been widely accepted, both by patients and by leprosy-control personnel; the three components—rifampin, dapsone and clofazimine—have been extremely well tolerated, and patient compliance has been at least as good as in the days of dapsone monotherapy. The main difficulties have been in the reliable delivery of the drugs to the patients by the leprosy-control infrastructure; however, MDT has proved to be operationally feasible where the infrastructure is adequate. Relapses have been remarkably few in the short term—fewer than 1% per year, despite the persistence of viable *Mycobacterium leprae* in a significant proportion of patients after MDT for 1 or more years, and caseloads have been substantially reduced in many areas.

Drugs of two additional classes exhibited bactericidal activity against *M. leprae.* Two fluoroquinolones—pefloxacin and ofloxacin—are fully active against *M. leprae* in mice; pefloxacin is rapidly bactericidal in patients with previously untreated lepromatous leprosy, and ofloxacin is currently in clinical trial. Minocycline, a lipid soluble tetracycline, is also fully active against *M. leprae* in mice, and is soon to be tested in man.

At this time, a number of important problems await resolution. A few patients with paucibacillary (PB) leprosy appear to be more appropriately treated by the regimen for multibacillary (MB) leprosy, but we are as yet unable to recognize these patients before treatment. The slow resolution of some PB lesions makes patients and staff unwilling to stop therapy, and it has been difficult to distinguish some late reversal reactions from relapse. The most effective way of using the new fluoroquinolones and minocycline to strengthen MDT has not yet been established, and the potential role of immunotherapy remains unclear. The potential role in leprosy control of rifampin as chemoprophylaxis has not yet been assessed, and measurement of the impact of MDT upon transmission of *M. leprae* in the community is made much more difficult by the lack of a reliable test for latent infection. There is a continuing need for new bactericidal drugs that are well tolerated and not prohibitively expensive, especially if they are suitable for intermittent, supervisable administration. Sensitive and reliable *in vitro* methods of detecting viable *M. leprae*

and measuring their susceptibility to drugs are needed to aid the assessment of treatment outcome and to facilitate the screening of new compounds. It is hoped that application of the techniques of molecular biology will assist in the achievement of these goals, and suggest new, potentially useful approaches to the cultivation of *M. leprae.*

During the next 5 years, MDT should be implemented in all countries for all patients. Simultaneously, the effectiveness of MDT over the long term must be assessed as precisely as possible. Special efforts should be undertaken to facilitate the distinction between reversal reaction and relapse, and relapse of MB leprosy must be documented whenever possible by inoculation of mice and drug-susceptibility testing. Trials of ofloxacin and minocycline should be mounted to measure the potential of these drugs for strengthening MDT. Work should be continued in the areas of the biology of *M. leprae* to better understand the action of the presently available drugs and to discover new targets of drug action. The search for additional new drugs should continue. The development of immunomodulating agents, including vaccines, should be pursued, both to strengthen chemotherapy and for immunoprophylaxis.

Efforts to cultivate *M. leprae* to assess the potential role of chemoprophylaxis and to develop means of detecting subclinical infection with *M. leprae* should be encouraged. Operational studies should be undertaken, particularly to find the most effective methods of delivering MDT in a variety of geographical and socioeconomic environments.