COMMITTEE 4: WORKSHOP ON EXPERIMENTAL CHEMOTHERAPY

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During the past five years, awareness has been heightened of the threat to leprosy control posed by drug resistance, especially resistance to dapsone. Secondary resistance to dapsone has been recognized wherever it has been sought. Moreover, organisms with a low degree of resistance to dapsone have been encountered in as many as 50% of patients with previously untreated lepromatous leprosy. Although these patients should nevertheless respond to treatment with dapsone in full dosage, this observation suggests an alarming situation.

The increasing prevalence of dapsone-resistant strains of *Mycobacterium leprae* requires that all multibacillary patients be treated with a combination of drugs. In addition to rifampin, clofazimine, and ethionamide or prothionamide, other well-tolerated bactericidal drugs are urgently needed. One of the major requirements for the development of new drugs is appropriate *in vitro* methods for screening large numbers of compounds for activity against *M. leprae.* A number of methods are currently being evaluated. For example, *"M. lufu"* is being used in the search for inhibitors of the dihydrofolate reductase of *M. leprae.* In addition, advances in our knowledge of the biochemistry of *M. leprae* may provide leads to other target enzymes.

The ubiquity of poor drug compliance emphasizes the importance of using drugs that are effective when administered intermittently under supervision.

Persistent *M. leprae,* i.e., drug-susceptible organisms that survive prolonged treatment by adequate therapy, have been detected in significant proportions of patients treated by a variety of multidrug regimens, among them regimens consisting of rifampin, dapsone, and clofazimine or prothionamide, each drug administered continuously in full dosage for two years. This suggests that no multidrug regimen is likely to eliminate persisting *M. leprae.* On the other hand, it is not certain that cure for multibacillary leprosy requires that all of the persisting organisms be killed. An eight-year follow-up of more than 300 multibacillary patients released from control after 20 years of well-supervised monotherapy with dapsone in full dosage yielded a relapse rate of only 1% per year. Among more than 100 multibacillary patients who had been treated with two years of intensive multidrug therapy after dapsone monotherapy of variable duration, no relapses were noted during a follow-up of 8–9 years. Thus, the use in leprosy control of intensive multidrug treatment of limited duration appears justified. Mathematical modeling may permit a more detailed understanding of the dynamics of the multibacillary patient's bacterial population during chemotherapy.