COMMITTEE 6: THERAPY

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"It has been said that it is now a practical proposition to control leprosy in this generation and eradicate it during the next. All that has to be done is to ensure that an adequate number of the correct pills pass down the throat of patients for a significant length of time"[14].

TREATMENT OF UNCOMPLICATED LEPROSY

Diaminodiphenylsulfone (DDS). The parent sulfone, DDS, continues to hold sway as the drug of choice in the management of uncomplicated leprosy; its low cost and the infrequency of the emergence of sulfone re-

sistant cases, when given in conventional doses, are its special features. Its slow bacteriostatic action and the consequent necessity to administer it over long periods of time and its inability to quickly clear the body of bacilli are some of its inherent drawbacks.

Under DDS therapy, even after the complete disintegration of bacilli in the skin, intact bacilli have been reported to be still present in smooth muscle and superficially located striated muscle [3], liver, bone marrow and lymph nodes. This may perhaps explain why relapses tend to occur even while the patient continues on the drug.

Unanimity has not been reached with regard to the optimum effective dose of DDS, frequency of administration of the drug, its relationship to the occurrence of reactive states and continuation of treatment after attainment of the inactive state, but the committee recommends treatment of lepromatous cases for life.

Other drugs. Less effective bacteriostatic agents such as thiambutosine, streptomycin and thiosemicarbazone are used less frequently in the treatment of leprosy.

Long-acting sulfonamides. These have the advantage of weekly administration by mouth. Some leprologists claim to have obtained good results with these drugs particularly in tuberculoid forms of the disease and its complicating neuritis. However, since serious and even fatal complications have followed the use of these drugs in the treatment of other diseases, the drugs should be used with caution in mass leprosy campaigns.

Clofazimine. A notable advance in the therapy of leprosy was the demonstration of the activity of clofazimine against *M. leprae*. The drug has bacteriostatic as well as anti-inflammatory properties.

The initial reports of Browne bearing out the anti-inflammatory properties of clofazimine [1] were followed by the demonstration of the antimycobacterial activity by Pettit *et al* [3] in the human, and by Shepard [10] in the mouse foot pad. The extensive clinical and experimental studies of Ross and his colleagues established the efficacy of clofazimine in sulfone-resistant cases. Clofazimine has established its value in the treatment of lepromatous leprosy but its high cost and the easy availability of the safe, effective and cheap DDS militate against its use in the treatment of uncomplicated lepromatous leprosy.

Diacetyldiaminodiphenylsulfone (DADDS). An initial short-term trial with this drug in the Philippines [11] and a subsequent longitudinal clinical trial in New Guinea [9] and Micronesia [13] have yielded satisfactory results. Although the initial reports regarding scheduled therapy in underdeveloped areas are encouraging, the possibility of the emergence of sulfone resistance, occurrence of relapses and the possible danger that this preparation may perpetuate a reactive state in cases in which the drug has triggered such a state have to be borne in mind.

Rifampicin. The newest entrant into the therapy of leprosy is a very potent antibiotic. Rees and his colleagues, after establishing its efficacy in mouse foot pad infection with *M. leprae*, used the drug in active and sulfone-resistant lepromatous cases [8] and found it effective. It is expected that the rapid killing of *M. leprae* will prevent the slow release of intracellular antigens of *M. leprae* and thus eliminate or markedly reduce the incidence of complications of immunocomplex deposition such as ENL. Although no toxic effects have been reported by these workers, there have been conflicting reports about its hepato-toxicity and the occurrence of thrombocytopenia [9]. In view of its high cost and limited availability, it would be wise to restrict its use to selected cases.

COMBINED THERAPY

Concurrent administration of drugs such as thiambutosine, long-acting sulfonamide, thiosemicarbazone, clofazimine and rifampicin along with DDS have been tried in the treatment of leprosy with a view to obtaining a synergistic effect and also to prevent the development of sulfone resistance. The results of the trials are not uniform—some found the combined treatment better than DDS alone, while others did not notice any substantial difference.

TREATMENT OF COMPLICATIONS ASSOCIATED WITH LEPROSY

Reactions in leprosy. With the advent of sulfone therapy, the incidence of the reac-

tive states has been on the increase with the manifestations becoming more severe and serious.

The first major breakthrough in the management of reactive states in lepromatous leprosy was the introduction of corticosteroid ([8]). Although this drug dramatically relieves the agony of severe reactions, the attendant undesirable side effects and drug dependence pose serious therapeutic problems.

The indication for the use of corticosteroids in the management of the distressing complications associated with leprosy has declined with the introduction of thalidomide ([12]). The effectiveness of thalidomide in controlling the acute exacerbations in lepromatous leprosy has been confirmed. In dimorphous and RTL reactions, it is reported to be much less effective. The major drawback of this drug is its teratogenic effect when administered to pregnant women.

While the consensus of opinion among workers is that the drug produces a spectacular effect in acute lepra reaction, there is no unanimity regarding the effect of the drug in neuritis, ocular and joint manifestations. In many instances these complications respond more readily to corticosteroid therapy, possibly because of its more generalized anti-inflammatory effect.

In recurrent lepra reaction, a maintenance dose of 50 mg to 100 mg/day of thalidomide is reported to keep the reaction under control. Further experience with the drug has shown that under its protective cover, steroid-dependent cases can be weaned from steroids and sulfone-sensitive cases continued on treatment with DDS.

With Browne's report of a possible anti-inflammatory action of clofazimine in lepromatous leprosy, a new era of hope opened up for lepromatous patients who were subjects of recurrent necrotizing reaction. The controlled clinical trials of Karat *et al* ([2]) confirmed the beneficial effects of the drug in lepra reaction. Similar reports have also appeared from Hastings, Warren and Trautman and many others. However, the beneficial effect of clofazimine takes as long as 8-12 weeks and sometimes high dosages, to become manifest and hence in severe cases with necrotizing lesions it will be necessary to combine clofazimine with corticosteroids or thalidomide until the acute phase is controlled. The significant improvements in the general health of these severely ill patients have been well documented.

While it is not effective in quickly controlling the acute reactive states, clofazimine has been observed to suppress not only the recurrent reactive episodes, but also permits withdrawal of steroid in steroid-dependent cases. Also it increases a tolerance to DDS in sulfone-sensitive cases while simultaneously exerting a beneficial effect on the disease process. Long-term studies are necessary to determine whether once the reactive states are controlled and the patient is able to take DDS in adequate doses, clofazimine can be withdrawn. It is a matter for serious consideration whether this drug could be safely used in cases of recurrent severe lepra reaction with overt renal involvement.

SULFONE RESISTANCE

The occurrence of drug resistance, one of the anticipated outcomes of chemotherapy, has now been well established in lepromatous cases ([13]) on DDS therapy. Inadequate dosage and irregular treatment appear to be contributing factors. This condition poses serious therapeutic problems. Clofazimine and rifampicin either alone or in combination with DDS (or other drugs such as thiambutosine and ethionamide) have been found to be effective in the management of these cases. However, emphasis should be laid on the prevention of this clinical state by adequate DDS therapy.

CHEMOPROPHYLAXIS IN LEPROSY

Chemoprophylaxis using DDS orally ([15]) and DADDS ([13]) has been found to yield satisfactory results. The value of chemoprophylaxis in the prevention of the development of lepromatous leprosy, its duration, the optimum dose and the frequency of administration are yet to be determined.

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