

A Century of Progress in the Therapy of Leprosy

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UNCOMPLICATED LEPROSY

Until the introduction of chaulmoogra oil and hydnocarpus oil in the latter half of the 19th century, patients with leprosy could only look forward to a state of "living death," ostracized by society and disowned by their kith and kin. The church took the lead at this stage effectively to translate into action the command "Love Thy Neighbor" by setting up leprosy homes, sanatoria and settlements. The legendary events on the island of Molokai, where Father Damien lived out this command to love, provide a vivid insight into both the hopelessness of the situation as it existed then and the frustrating limitations on what could be achieved even through the most devoted and selfless service. In dealing with leprosy sufferers, their isolation and segregation from the main stream of life into areas well away from human contact and habitation had become inviolable dogmas within the narrow confines of which methods of treatment and succour for these unfortunate patients had to be evolved. It would not be an exaggeration to say that a leprosy patient was looked upon as a "disease walking in the guise of man" rather than as a man with a disease. The Biblical references to leprosy, largely misunderstood, helped to further propagate the mythological fears about this disease.

The oral and later parenteral use of chaulmoogra oil, hydnocarpus oil and their derivatives was the first therapy of any effectiveness for leprosy, it being successful in arresting the disease over a period of time. This therapy is believed to have originated in the Orient, especially in India and China. During the first three decades of the twentieth century, the literature on leprosy is replete with reports of the therapeutic efficacy of chaulmoogra oil and its

derivatives. The largest trial was reported from Culion, Philippines (⁴) where, of a total of 3,133 patients under treatment, 77% were reported to have improved (including 8.4% who became negative), 11% were stationary and 11.5% became worse. Therapeutic trials round the world confirmed the efficacy of this therapy, though it was clear that patients needed years of parenteral therapy to attain bacteriological negativity and clinical cure of the disease.

At the same time as extensive trials of chaulmoogra and its derivatives were under way, a number of miscellaneous methods of treatment were also being tried with diverse and conflicting reports of success. Mention may be made of various dyes such as methylene blue, mercurochrome, gentian violet etc.; assorted vaccines; heavy metals, e.g., mercury, gold, silver, arsenic, antimony etc.; and foreign protein. Some of these methods of treatment were seen to produce *erythema nodosum leprosum* which was considered by the majority of physicians of the time to have beneficial effects on the disease process itself, without recognizing the irreversible damage to peripheral nerves, eyes, reticulo-endothelial system, endocrine glands and kidneys caused by these showers of evanescent skin lesions.

The world was pleasantly surprised when Faget (⁵) reported from Carville, U.S.A., in 1942, the rather dramatic results obtained with a derivative of diamino-diphenylsulfone, PROMIN, in patients with advanced lepromatous leprosy. He reported on the effect of intravenous injections of PROMIN in doses ranging from 0.4 gm to 5.0 gm daily, with an average dose of 1.0 gm to 2.0 gm per day, six days in a week. In patients given less than 500 mg to 1000 mg per day 72.5% showed marked improvement in clinical and bacteriological status. Further, among those who completed one year of treatment, 10% became bacteriologically negative and remained negative on consecutive examinations. The lepromatous nodules shrank, epistaxis and blocking of the nose ceased; there was marked improve-

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ment in leprous laryngitis and tracheostomies became unnecessary; eyebrows were noticed to regrow; there was improvement and more than 50% of lepromatous leprosy patients attained skin smear negativity. The results obtained by Faget were later confirmed by Fite (¹⁰), Wharton (⁴⁰) and others.

The main toxic effect noticed with PROMIN was depression of the bone marrow with resultant anemia and leucopenia which reverted to normal after cessation of therapy. The need for daily parenteral administration was another major limitation. The search for suitable substitutes for PROMIN, which would be less toxic and yet be active against *Mycobacterium leprae* when taken by mouth, led to the use of Diasone which was found to be equally effective when administered orally in doses ranging from 0.3 gm to 1.0 gm per day, and clinical improvement was noted in six months (^{6, 23}). Faget (⁷) suspected that the diamino-diphenylsulfone in each of these compounds was the active principle, and clinical trials with dapsone (DDS) confirmed his suspicion. It was further noted that dapsone, when administered in doses of 100 mg per day, six days a week, was remarkably free of toxic side effects though therapeutically it continued to be no less effective. During the last twenty-five years, dapsone has become the universally accepted standard treatment for leprosy.

Controversy regarding the optimum effective dose of dapsone has been raging in the leprosy world ever since experimental studies of the inhibitory action of dapsone in homeopathically small doses in the foot pads of mice was demonstrated eight years ago (³³). In certain places therapeutic enthusiasm seems to have out-stripped therapeutic judgement, the pendulum having swung too far in favor of small doses of dapsone, with the potential danger of the development of sulfone resistant strains of *M. leprae*. It is highly desirable and wise to keep the dose of dapsone at 150 mg to 300 mg per week in divided doses.

The results of the therapeutic and experimental trials of repository preparations of the monacetyl derivative of dapsone (DADDS) have been encouraging, espe-

cially in situations as obtain in Karimui (³¹), New Guinea, where inaccessibility of patients for treatment poses a major problem and therefore one injection once in seventy-five days is certainly attractive. However, in such conditions one awaits with bated breath the possibility of the emergence of strains of *M. leprae* resistant to dapsone. Meanwhile, the enthusiastic advocacy of these infinitesimally small doses of dapsone for routine treatment of leprosy should be deprecated.

With the introduction of dapsone a quarter of a century ago, the first real hope of ultimate recovery from leprosy appeared on the horizon. However, over the years it has slowly become clear that dapsone, while being an effective bacteriostatic agent against *M. leprae*, acts very slowly and needs to be administered over a prolonged period of time.

Another disturbing feature of the post-sulfone era has been the appearance of a rather high incidence of "reaction" (ENL, acute neuritides, iridocyclitis) ranging from 30% to 70%, the rate varying with different ethnic groups. Further, a number of patients entered a phase of recurrent or chronic reaction and could not be treated with any sulfone derivative. An occasional patient developed hemolytic anemia or exfoliative dermatitis. Mild derangement of hepatic function and an occasional case of psychotic behavior was also reported.

However, to date there has been no substitute equal to dapsone which has stood the test of time, and being very cheap it is within the means of patients in endemic areas, who are generally economically backward.

After the Second World War, a whole range of chemotherapeutic agents and antibiotics became available for the management of bacterial infections. Many therapeutic trials of these in leprosy were conducted with enthusiasm, especially with antituberculous drugs and antibiotics. On the whole, none of them were found to be particularly effective in leprosy except in special situations, and hence dapsone retained its claim to be the most effective therapeutic agent in the treatment of leprosy. However, some of these other agents

merit an individual mention.

Diphenyl-thiourea (Ciba 1906) was introduced two decades ago with the claim that it was an effective antileprosy drug without the disadvantages of dapsone. It was said to produce a lower incidence of ENL, neuritis and eye complications than that seen among patients treated with dapsone. While it is true that this drug caused a lower incidence of ENL and acute neuritides, it was soon found to be a less effective bacteriostatic agent against *M. leprae* and to lead to the appearance of resistant strains of *M. leprae* at between 18 to 30 months after initiation of treatment. It is being used less and less, especially during the last five years. It may still have a place in the management of patients who are intolerant of other effective antileprosy drugs.

Streptomycin. Daily injections of streptomycin were tried in leprosy patients by several workers and found to have a temporary beneficial effect. Karat *et al* (16) suggested that streptomycin was of particular benefit in patients with active leprosy ulceration of the skin, leprosy laryngitis with hoarseness of voice, leprosy rhinitis, and acute leprosy lymphadenitis complicating the ENL syndrome. Hastings and Trautman (11) reported the efficacy of combined therapy using sulphone and streptomycin in the treatment of relapsed lepromatous leprosy, suggesting a synergistic effect of streptomycin with sulphone.

Thiosemicarbazone (Thiacetazone). Another drug used widely in the management of tuberculosis was reported by Ryrie (32) to be effective against all varieties of leprosy. It was also noted that the incidence of ENL reactions and acute painful neuritis was less in these cases than in the DDS treated group. The efficacy of thiosemicarbazone as a bacteriostatic agent against *M. leprae* was further confirmed in the foot pads of mice. However, in long term trials it was found that *M. leprae* began to develop resistance against thiosemicarbazone between 18 to 30 months of exposure, and hence this drug did not really make a major contribution to the therapeutic armamentarium in leprosy except as a temporary measure to tide over a

"crisis" situation. The ever present hazard of agranulocytosis and a 10% incidence of peripheral neuropathy reported in trials in tuberculosis are added deterrents to the widespread use of this drug in leprosy.

The other antituberculosis drugs such as ethionamide, isoniasid, PAS, cycloserine and pyrazinamide were not sufficiently active against *M. leprae* to attain clinical significance.

Long acting sulfonamides (sulfor-methoxide or Fanasil; sulfamethoxy-pyridazine or Lederkyn). During the last decade this group of drugs underwent extensive trials in Africa and India, the main attraction being the possibility of a single weekly dose in mass treatment campaigns, and the lower incidence of ENL and leprosy neuritis that were reported. The most favorable reports were from Languillon (22) who claimed clinical and bacteriological improvements in twelve months, a milder form of *erythema nodosum leprosum* not requiring interruption of treatment and relief of neuritic pain. Ramanujam (28), on the other hand, found that Fanasil is not as effective as standard dapsone treatment, and in his study 66% of lepromatous patients underwent reactional episodes. Further, the possibility of *erythema multiforme* or agranulocytosis appearing in these patients makes it an unlikely choice for general use among leprosy patients.

Antithyroid drugs made a sporadic and unsuccessful appearance on the scene of therapy of leprosy patients but were found to be ineffective.

Clofazimine. The next major advance in the therapy of leprosy, after the introduction of sulfones in the forties, was the demonstration of the activity of clofazimine (Lamprene, B663), a rimino-phenazine derivative, against *M. leprae*, which appeared to combine in itself the bacteriostatic effect of dapsone with the anti-inflammatory effects of steroids. The initial reports of Browne (2) were confined to the efficacy of clofazimine in suppressing ENL reaction in lepromatous leprosy. The pilot trial of Pettit *et al* (26), using morphological changes in *M. leprae*, the fall in the biopsy index and the clinical response as criteria of antibacterial activity, indicated that clofaz-

imine was an active antileprosy drug causing leprosy bacilli to become irregularly strained, and presumably killing the bacilli. The ability of clofazimine to kill *M. leprae* was further confirmed by Shepard⁽³⁴⁾ using the mouse foot pad model. The controlled longitudinal clinical trial of the efficacy of clofazimine in lepromatous leprosy by Karat *et al*⁽¹⁹⁾ showed that at a dose of 100 mg daily, clofazimine was as effective as dapsone in bringing about bacteriologic and clinical remission of lepromatous leprosy, accompanied by striking improvement in neurologic functions⁽²¹⁾. Regrowth of eyebrows, striking improvement in the general condition of the patients as judged by rise in serum albumin, hemoglobin values and body weight are added features of the beneficial therapeutic effects of this agent.

The most distressing side effect of clofazimine is the development of a deep brownish-red pigmentation of the skin and conjunctiva with associated dryness, scaliness and fissuring of the skin (ichthyosis) which patients as a rule dislike. Brownish discoloration of sweat and urine and occasional diarrhea, especially when doses of more than 300 mg per day are used, are less important side-effects. To date, no embryopathy, following administration of clofazimine to women throughout pregnancy, has been reported.

With the emergence of strains of *M. leprae* resistant to DDS, leprosy was recognized once again as becoming an untreatable disease. Into this threatened therapeutic vacuum clofazimine made its entry. The extensive clinical and experimental studies of Pettit and Rees⁽²⁴⁾ have established firmly the efficacy of clofazimine in this situation, and so far there have been no reports of *M. leprae* developing resistance to clofazimine.

The role of clofazimine in the management of reactive episodes of leprosy will be discussed later.

Rifampicin. The newest entrant into the therapy of leprosy is rifampicin² a very

potent antibiotic, found to be most effective against *M. tuberculosis*. Rees and his colleagues⁽²⁰⁾, after establishing the efficacy of rifampicin in mouse foot pad infections with *M. leprae*, studied the effect of a daily single dose of 600 mg of rifampicin in six untreated lepromatous leprosy patients. They observed a precipitous fall in the Morphologic Index at a rate much faster than what had been previously observed with any other antileprosy drug. Extended trials confirmed the initial findings, and no toxic effects were encountered. Rifampicin appears to be the only rapidly acting, effective, bactericidal drug currently available against *M. leprae* injections, and holds much promise for the future. It is expected that the rapid killing of *M. leprae* would prevent the slow release of intracellular antigens of *M. leprae* and thus eliminate or markedly reduce the incidence of complications of immune-complex deposition such as the *erythema nodosum leprosum* syndrome. It has been further demonstrated that *M. leprae* which are resistant to dapsone are still very sensitive to rifampicin and, therefore, at the moment it would seem wise to deliberately restrict the use of this drug to patients who have dapsone resistant strains of *M. leprae*. In any case the high cost and very limited supply of rifampicin currently available for clinical use may facilitate the judicious use of this most promising drug against *M. leprae*.

COMPLICATIONS ASSOCIATED WITH LEPROSY

Reactions in lepromatous leprosy. From Armauer Hansen's time, the occurrence of "reaction" in leprosy, characterized by showers of evanescent erythematous skin nodules associated with fever and/or painful enlargement of peripheral nerves with or without development of neurological deficit, painful eyes due to iridocyclitis joint pains, tender enlargement of lymph glands, edema of the feet, etc., have been well-known. For over half a century heavy metals (e.g. gold) and antimonials held sway in the management of this distressing complication of lepromatous and near lepromatous leprosy, with assistance from salicylates.

² Clinical trial in leprosy first reported by D.V.A. Opromolla at VIII International Congress of Leprology, 1963. *Internat. J. Leprosy* 31 (1963) 552. Expanded report: *Leprosy Rev.* 36 (1965) 123-131. —Editor.

The parenteral use of fluorescein group of dyes was also in vogue. However, the parenterally administered antimonials (e.g., potassium antimony tartrate, Stibophen, Fouadin, etc.) have found a definite place in the management of less severe forms of reaction over the years, and are fairly widely used even today.

Salicylates, apart from their analgesic and antipyretic effects, seem to help to control the milder forms of reaction and have been joined by Paracetamol in the last decade. On the whole, indomethacin in reactions has been disappointing except for the beneficial effect observed in patients with ocular complications (¹⁷). About two decades ago 4-amino-quinolines (chloroquin, Camaquin, Nivaquin) were introduced in the management of reactions in leprosy (²⁷). This group of drugs was found to have therapeutic effects comparable to parenterally administered antimony preparations and to that of indomethacin, aspirin and Paracetamol. They were found to be particularly suited for use in mass, domiciliary treatment and leprosy control programs mostly managed by medical auxiliaries. On a short-term basis (up to 12 weeks) they can be safely administered by nonmedical leprosy workers. The dose may vary from 200 mg to 600 mg of the base per day according to clinical needs. However, gastrointestinal intolerance limits the usefulness of the drug and ocular complications lay heavy responsibility on the leprosy worker to ensure that vision is not jeopardized by injudicious, prolonged use of this drug.

The first major break-through in the management of severe reactions in all types of leprosy occurred with the use of corticosteroids (^{15, 30}). The hitherto untreatable patients with recurrent necrotizing ENL, chronic ENL, and Lucio phenomenon, who could only hope to find some relief of symptoms by analgesics, were now able to get their distressing and painful problem under control, on occasion albeit with large doses of corticosteroids with their attendant side effects.

The indications for the use of corticosteroids in complications associated with leprosy have declined with the introduction

of thalidomide and clofazimine, and even when indicated, the effective dose has come down greatly by virtue of the steroid sparing effects of thalidomide and clofazimine.

At the present time, except in the Lucio phenomenon, the control of severe toxic state during reactions, acute ocular complications threatening vision and in acute neurological catastrophes associated with all types of leprosy, there is little justification for the exhibition of corticosteroids in the management of leprosy.

The discovery of the effectiveness of thalidomide in reactions in leprosy about a decade ago by Sheskin (³⁵), and his colleagues in Israel was the next landmark in the search for effective therapy of this dangerous and difficult phase of lepromatous leprosy. Therapeutic trials round the world have confirmed the efficacy of thalidomide in reactions in lepromatous leprosy, including the recently reported WHO coordinated double-blind trial (¹⁴). The most commonly used dose is 100 mg thalidomide three to four times a day. Obviously, because of the rather high risk of embryonopathies when administered to pregnant women, this drug must be used exclusively in males except where female patients have either been sterilized or are under vigilant, institutional supervision. Further, thalidomide must not be used without adequate specific antileprosy chemotherapy since it has been well-established that while thalidomide is effective in controlling the manifestations of reaction in lepromatous leprosy, the primary disease itself worsens as judged by the rise in Bacterial and Morphologic Indices (³⁶).

The most promising drug to appear in this therapeutic vacuum in the effective management of reactions was clofazimine. With Stanley Browne's report in 1965 of a possible anti-inflammatory action of B663 in lepromatous leprosy (²), a new era of hope opened up for lepromatous leprosy patients with recurrent and necrotizing chronic ENL syndrome. The controlled clinical trials of Karat *et al* (¹⁸) confirmed the striking beneficial effect of 300 mg of clofazimine per day as compared with 30 mg of prednisolone per day in severe ENL.

Today there is no doubt about the efficacy of clofazimine not only in patients with severe, necrotizing *erythema nodosum leprosum* but also in patients with severe recurrent or chronic *erythema nodosum* (12, 38). However, the optimum effects of clofazimine appear slowly over a two to four week period and hence in the severe cases and in necrotizing lesions, it may be advisable to combine clofazimine with 20 mg to 30 mg of prednisolone for two to four weeks till the acute phase is controlled.

Karat and associates (18, 21) have also documented the significant improvement in the general health of these considerably ill patients, as judged by significant weight gain, rise in hemoglobin and serum albumin and improvement in renal function as well as in peripheral nerve function.

Clofazimine appears to be the drug of choice in lepromatous leprosy complicated by severe reaction, including acute leprous peripheral neuropathy. Clofazimine has also been shown to have a prophylactic effect in suppressing recurrence of reactions after the control of the acute episode (20).

Drug resistance. One of the possible outcomes to be anticipated in chemotherapy of leprosy is the emergence of drug resistance in *M. leprae*. Such drug resistance can arise in one of three ways: a) as a result of the causative organism being exposed to subminimal inhibitory concentration of the drug consequent on the drug being taken irregularly or in inadequate doses, or owing to malabsorption of the drug when taken by the oral route; b) following relapse of the disease the causative organism may not respond as favorably to the same drug as it did at the time of initial treatment with the drug owing to the fact that the organism has already been exposed to the drug in an earlier phase of the disease; and c) as a result of the development of mutant strains of the causative organism. Emergence of resistance against one or more drugs used in the chemotherapy of leprosy bring in its wake serious therapeutic problem with respect to the management, not only of these cases, but possibly of those cases arising in sub-

jects to whom the drug resistant cases have served as the source of infection.

In these twenty-six years of chemotherapy of leprosy with dapsone, genuine sulfone resistance has not developed in sufficiently serious proportion to cause alarm. This is perhaps largely due to the administration of dapsone in more than adequate doses in the past. In recent times, however, the increasing tendency on the part of the leprologist to indulge in smaller and smaller doses of dapsone in the treatment of lepromatous leprosy certainly holds out the grim prospect of the development of sulfone resistance in the not too distant future. Except for vague suspicions expressed occasionally about the occurrence of drug resistance in leprosy, serious thought was not given to it nor its presence established until Pettit and his coworkers (25) in 1960 drew pointed attention to the occurrence of this state by a well-documented paper. For the first time, they demonstrated and established laboratory procedures whereby the development of drug resistance could be established on firm grounds.

Suspicion about the development of sulfone resistance especially in lepromatous cases first arises from clinical observations. It is well-known that in the moderately and highly advanced cases of lepromatous leprosy clinical improvement sets in after about three to six months of adequate dapsone therapy. Lack of such clinical response, and sometimes occurrence of clinical deterioration while under treatment, should arouse the first suspicion of the possible development of sulfone resistance. With the improved laboratory techniques now available, the suspicion of drug resistance can be confirmed by instituting certain laboratory procedures. One such procedure which is well within the scope of all leprosy treatment centers with facilities for bacteriological examination is the determination of the Morphologic Index (MI), i.e., enumeration of the percentage of solid staining bacilli in the skin smears. It has been observed by Waters *et al* (30) that the therapy of lepromatous case with antileprosy drugs of proven therapeutic value brings down the MI to less than 5% in the course of six to nine months. If, in a given case of

lepomatous leprosy receiving a potent antileprosy drug, the MI does not come down to less than 5% in the above specified period, or there is a progressive increase in the MI after an initial fall, the indication is that the organism is resistant or becoming resistant to that particular drug. A more sophisticated method of demonstration of drug resistance is to use mouse foot pad infection. This method, though more decisive, can be practiced only in specialized institutions and is also time consuming.

At the present time, two drugs are available for the management of these sulfone resistant cases, viz, clofazimine and rifampicin. Pettit *et al* (²⁴) found that clofazimine yields satisfactory clinical, bacteriologic and histologic improvement in sulfone resistant cases. Rifampicin has also been reported to be useful in the management of sulfone resistant cases (²⁹). But these drugs are expensive and not freely available yet. Hence, the emphasis is laid on the treatment of lepomatous cases with adequate doses of dapsone in order to prevent the occurrence of sulfone resistance.

PROPHYLAXIS IN LEPROSY

Although the introduction of sulfone in the treatment of leprosy has proved to be a powerful weapon in the control of the disease, the lack of motivation for treatment and the disadvantages incumbent upon the long period of treatment necessary to make an open case inactive, naturally drew the attention of workers to the application of prophylactic measures in the control of leprosy. As in tuberculosis, so in leprosy, two methods of inducing prophylaxis are theoretically available, immunoprophylaxis and chemoprophylaxis, and efforts have been under way to assess the protective value of these two measures.

Immunoprophylaxis. Thoughts on immunoprophylaxis arose as far back as 1939, when Fernandez (⁸) observed that administration of BCG vaccination tended to convert lepromin-negative to lepromin-positive response in leprosy contacts and suggested that as such BCG might confer some protection against leprosy. Oral administration of BCG was found to be a practical, easy and harmless method of activating the Mit-

suda reaction in the healthy. The first observations on the value of BCG vaccination as a prophylaxis against leprosy came from Fernandez (⁹) in 1951, who found that vaccination with BCG does not confer absolute protection against leprosy but a relative one, "sufficient degree of resistance being established so that if the disease does develop it will be of a benign form." In the wake of the observations of Fernandez came the preliminary report of de Souza Campos (³) who found that after the administration of BCG orally in a dose of 200 mg once a week for three consecutive weeks, the incidence of leprosy in the vaccinated group was 0.6%, all of them tuberculoid cases, while in the unvaccinated group the incidence was 5.4%, and 26.3% of these were lepomatous. He concluded that, "BCG vaccination clearly has a protective effect as regards leprosy infection." Since the publication of these results further trials with BCG vaccination in the prevention of leprosy have been carried out.

Of the several such trials, three controlled field trials need special mention (⁴¹). The first trial was initiated in 1960 in Uganda on child contacts and relatives of mostly tuberculoid cases, the second in Eastern New Guinea in 1962 in an aboriginal population of all ages with a high incidence of tuberculoid leprosy and low incidence of tuberculosis, and the third under the aegis of WHO in Burma in 1964 to determine the protection conferred on the general child population in a highly endemic area having a higher proportion of lepomatous leprosy than Uganda. The findings of these three field studies were that "in Uganda BCG vaccination conferred protection against early forms of leprosy for a period of three years or more in about four-fifths of the children exposed to intrafamilial risk," in New Guinea "it provided no unequivocal protection of exposed individuals," while the Burma trial showed "no significant difference in the pattern of leprosy incidence in the two groups nor did BCG have any appreciable effect on the forms of leprosy that did develop in both the groups" (¹). In view of these findings, the Expert Committee on Leprosy

of WHO in 1970, considered it premature to recommend BCG vaccination for the protection of leprosy and found it advisable to extend the trial for at least ten years.

Chemoprophylaxis. Suggestive evidence of the prophylactic value of DDS was first reported by Figueredo and his coworkers in India⁽¹³⁾ and Laviron in Africa. A double-blind chemoprophylaxis trial carried out at Chingleput, India, on children under 15 years of age who were living in contact with bacteriologically positive cases of leprosy, using DDS as prophylaxis orally almost in conventional doses, showed that under the conditions of the trial this procedure brought about a reduction of 52.5% attributable to chemoprophylaxis; and none of the cases that arose in the contacts were lepromatous⁽⁴²⁾.

The interim results of another controlled chemoprophylaxis trial in child contacts under ten years of age in Culion, Philippines, using half to two-thirds of the dose of DDS used in the Chingleput study, showed at the end of three years an estimated reduction of 44% attributable to chemoprophylaxis⁽⁴²⁾.

The value of chemoprophylaxis in the development of lepromatous leprosy is yet to be determined; and so are the duration of prophylaxis, the optimum dose and the frequency of administration.

The results of a chemoprophylaxis trial using DADDS, a repository preparation of a derivative of DDS obviating the problems incumbent upon the use of DDS orally over a long period of time, have come from Sloan and his coworkers⁽³⁷⁾, who using acedapsone parenterally once in 75 days over a period of three years in the exposed population, found that the occurrence of new cases was brought down to one-sixth of that expected.

The application of immuno- and chemoprophylaxis in leprosy have their own advantages and disadvantages. If BCG vaccination is established to be effective in the prevention of leprosy, it will be a big step forward since it will offer protection against both tuberculosis and leprosy and will be capable of wider and easier application.

Concluding remarks. From the bleak era of utter hopelessness and despair of a centu-

ry ago the therapy of leprosy has moved forward a long way in impressive strides, especially over the last 25 years. Whereas 25 years ago one could barely hope for an arrest of the disease in a fortunate few while on chaulmoogra or hydnocarpus derivatives, today one can confidently state that leprosy can be cured.

Patients with leprosy need no longer walk alone. They have valiant and dedicated companions among the pharmacologists and physicians in some of the best research and treatment centers in the world. The leprosy bacillus has been dealt a mortal blow. It is to be hoped that existing knowledge will be put to judicious and effective use in the service of leprosy patients. Neither therapeutic enthusiasm nor therapeutic nihilism are likely to yield significant dividends. One looks forward to the coming years with the hope that chemotherapeutic agents, more effective and more deadly to the leprosy bacillus, may be found which would enable us to heal the patient faster.

The uncertainty and the extreme test of patience that continue to be part of the best treatment currently available have been no inconsiderable part of the unconscionable weight of unmerited suffering and hopelessness that has bowed down the leprosy patient for ages. Hoary social and cultural attitudes change slowly but there can be no doubt that a sure and faster cure will greatly hasten the rehabilitation of the leprosy patient in the hearts and homes and the daily commerce of the human family.

Acknowledgements. We are deeply indebted to Mr. G. R. Karat, M.A., Associate Director, Christian Institute for the Study of Religion and Society, Bangalore, South India, for helpful criticism and encouragement as well as for patient correction of the manuscript.

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