CLINICAL EVALUATION STUDIES OF THE LEONARD WOOD MEMORIAL

Objectives, Methods and Conclusions[1]

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Sulfones were first used in the treatment of leprosy about 20 years ago by Faget and associates at the Public Health Service Hospital, Carville, Louisiana. Although they have gradually replaced the chaulmoogra preparations as standard treatment for leprosy, the earlier optimism regarding their effectiveness has been tempered by experience. At best, sulfones are bacteriostatic rather than bactericidal. They are ineffective in some cases, and in others relapses have been found to occur after apparent arrest. Obviously, therefore, the sulfones are not the final goal in the chemotherapy of leprosy.

The search for better therapy has been made more urgent by the great extension of outpatient treatment of millions of leprosy cases all over the world. Unless more effective drugs are discovered, hopes of eradicating leprosy through chemotherapy will not be realized. Proof of value of any treatment, however, can be obtained only by controlled clinical trials. In leprosy, adequate controls are imperative, because its slow natural course tends toward inactivity with occasional exacerbations and remissions. Available measures of clinical and bacteriologic changes are far from precise. Acceptable evidence of the value of any method of treatment, and of the superiority of one drug over another, can be obtained only by study of matched groups of patients, each of sufficient size to permit separation of the frequency of improvement attributable to therapy from that due to natural causes.

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PROCEDURES AND METHODS

Objective.—The major objective of the studies was to find a drug or antibiotic giving definite clinical and bacteriologic improvement, which would prove more efficacious than the sulfones within a period of one year. The hope of dramatic effect was minimized; the impelling motive was to detect smaller and less obvious advantages of one treatment over another, which, however, would be of incalculable value when applied to very large numbers of patients.

Cases included in the studies.—Only patients in whom the disease was diagnosed as lepromatous, who were negative to lepromin and whose lesions were positive bacteriologically, were admitted. Limitation to the lepromatous type of the disease provides a more homogeneous patient body from which to choose the therapy groups. There is also much less natural fluctuation than in the nonlepromatous types.

Numbers of patients required.—From 40 to 60 patients in each therapy group were entered in each study at each institution. These numbers were the minimum expected to yield statistically valid differences in the proportions of cases becoming completely negative bacteriologically at all sites; that is, between patients under sulfone therapy, of whom fewer than 10 per cent are expected to become negative after 48 weeks of therapy, and those under a superior drug which might cause 30 per cent or more to become negative.

Assignment of patients to therapy groups.—The most important preliminary procedure was the unbiased assignment of patients to the respective therapy groups. The objective was to obtain matched groups that would show, on the average, the same degree of responsiveness to a specified therapy. Such factors as sex, age, stage of the disease and prior sulfone therapy were always considered because each might have some possible prognostic significance. In all the studies, however, there has been no definite evidence that any of these background factors is associated unduly with clinical or bacteriologic improvement after subsequent therapy.

In the assignment to therapy groups, index cards for patients of each sex were first arranged in order of decreasing age and distributed to the group, using a table of random numbers. Revisions were then made until a good balance was obtained with regard to all of the background factors named above.

Patients treated previously with sulfones were kept without treatment for a minimum period of two months before the start of each new series. In the fifth and sixth series all save a very small proportion of the patients were previously untreated.

Dropped patients.—The problem of discontinuance of therapy occurs in every prolonged study. It is essential to record in every instance the reason for discontinuance and the date. Death and illness from causes other than leprosy occurred without preference in all the therapy groups. Patients who showed intolerance to a drug or worsening of the disease were withdrawn and, practically speaking, completed therapy at the time of withdrawal. The records of their physical condition and bacteriology for the date closest to time of withdrawal were taken as final. The greatest problem was the departure of patients from the leprosarium without permission. A careful reappraisal made at the end of each series, however, showed that the dropped patients did not affect sufficiently those factors considered important in the original matching.

Measurement of results.—To avoid any unconscious bias toward a particular treatment the clinical examinations of patients were made by outside consultants. Patients were brought in for examinations in a random order without reference to therapy group or laboratory findings. In the fourth, fifth and sixth series the principle of the "double-blind" experiment was adopted, with use of elaborate systems of placebos to match the trial drugs. In these three series neither clinicians nor patients knew the nature of the therapy given any group.

At each examination, a dermatologic and neurologic appraisal of the whole body was made. An attempt was made to grade and give numerical value to infiltration, nodules, plaques, extent of anesthesia, and certain other signs on each of several parts of the body. At the end of the final examination, the consultant entered his opinion

regarding the clinical changes, as improved (Sl., Mod. or Mk.), stationary, or worse (Sl., Mod. or Mk). Colored and black and white photographs taken before therapy aided the consultant in making a decision regarding dermatologic changes.

Bacteriologic procedures were standardized as far as possible, but the point on which greatest emphasis was laid was that the technic used must be exactly the same on subsequent examinations as in the preliminary one. Except for unavoidable changes, the smears were taken and examined by the same person on each occasion. Eight sites, viz., each earlobe, each side of the nasal septum and four optimal skin sites, were included in each examination.

Although complicated statistical analyses were made of the bacteriologic findings, including methods of variance and co-variance, the basic procedures were simple. Correlation tables were prepared for each therapy group, for all sites and for nasal and skin sites separately, showing the frequency of sites falling into each of the several categories (recorded as negative, very scanty, 1+, 2+, 3+ and 4+) for the preliminary examination on one axis (ordinate), and for the final examination on the other (abscissa). An average bacteriologic score was readily obtained from such a table. The following weighted values were used: v.s. = 1; 1+ = 2; 2+ = 3; 3+ = 4; 4+ = 5. The numbers in each category were multiplied by these weights for the preliminary and final examinations, respectively, summed and divided to obtain the average score.

As stated previously, the possible prognostic importance of sex, age, stage of the disease and previous sulfone therapy was constantly scrutinized in the statistical analyses of clinical and bacteriologic findings.

In addition to careful matching of therapy groups and impartial clinical appraisal by outside clinicians, a valuable safeguard in these studies was that identical experiments were always conducted in two or more institutions.

STUDIES COMPLETED

First series (1952-53).—Four leprosaria participated in the first series: Aisei-en and Komyo-en in Japan, Eversley Childs in the Philippines, and Westfort in South Africa.[2] The drugs and combinations tested were: (A) Diasone (Diamidin); (B) 4-4′ diaminodiphenyl sulfone (DDS); (C) dihydrostreptomycin (DHSM) sulfate; (D) Diasone plus DHSM; (E) DHSM plus sodium p-aminosalicylate (PAS) and (F) a placebo (Ceslu) at Aisei-en and Komyo-en and Eversley Childs, and PAS at Westfort. The maximum dosages used were: Diasone 1 gm. daily; DDS 0.2 gm. daily; and DHSM 1 gm. three times a week. No treatment was given on Sundays. The identity of Ceslu, a placebo of inositol and glycine, was withheld until the end of the study. Duration of therapy was 32 weeks at the Japanese institution and 48 weeks at Eversley Childs and Westfort.

The following conclusions were reached, based upon records of 312 patients who completed therapy at Aisei-en and Komyo-en combined, 307 at Eversley Childs and 233 at Westfort. Diasone, DDS, and DHSM were shown to be of definite and apparently of equal value in the treatment of lepromatous leprosy, insofar as could be judged from clinical changes during therapy. A combination of DHSM and Diasone showed no advantage over Diasone given singly, and the addition of sodium p-aminosalicylate (PAS) did not increase the effectiveness of DHSM. The proportion of patients definitely improved was substantially higher for groups (A) to (E) than for the control groups. The

proportion definitely worse was likewise much higher for the placebo group than for the other groups. Moderate or marked clinical improvement occurred in a few patients in the placebo group, and in a large proportion of these untreated patients the clinical condition remained stationary for many months, constituting definite proof of the necessity of controls in studying the effect of drugs in lepromatous leprosy.

In general, bacteriologic improvement was definitely greater for all therapy groups (A) to (E) than for the control group, especially in the Philippine and Japanese institutions, where the latter group was given a placebo. None of the therapy groups (A) to (E) was significantly different from any other in respect to bacteriologic changes. In the control groups, the proportion of sites showing bacteriologic improvement was substantial at all centers, indicating that such improvement is attributable to causes other than specific therapy. There was no appreciable change in the lepromin status of the patients after therapy.

Second series (1953-54).—Small groups of patients had been previously treated with isoniazid INH) without striking results.[4] It was considered, nevertheless, that a larger experiment was necessary to assess the value of INH in combination with other drugs. Accordingly, the drugs and combinations tested in the Second Series were: (A) Diasone; (B) Diasone plus INH; and (C) INH plus dihydrostreptomycin. The maximum dosages used were: Diasone 1 gm. daily; INH 10 mgm. per kgm. of body weight daily; and DHSM 1 gm. twice a week. No treatment was given on Sundays. Participating institutions were: Central Luzon and Eversley Childs, Philippines, and Westfort, South Africa.

From the records of 187 patients completing 48 weeks of therapy at Central Luzon, 202 at Eversley Childs and 111 at Westfort, it was shown that at all institutions, treatment with both INH and Diasone or with both INH and DHSM gave no better clinical results than were observed with Diasone alone. Bacteriologic improvement occurred likewise in a high percentage of sites in all therapy groups at each institution, but was more or less the same in each therapy group. Very few patients became negative at all of the eight required sites, and in this respect also there was no association with any therapy. The conclusion was reached that in all probability much of the bacteriologic improvement observed was not attributable to any therapy but to unknown causes equally operative in all groups.

Third series (1955-56).—The specific objectives of the third series[5] were to compare the effectiveness in lepromatous leprosy of 4-4″ diaminodiphenyl sulfone (DDS) with that of DDS plus nicotinamide; and the benefit, if any, of supplementing either of these therapies by vaccination with BCG. Nicotinamide had previously been demonstrated to be very effective in rat leprosy. Participating leprosaria were: Central Luzon and Eversley Childs, Philippines, and Westfort, South

Africa. Two major groups of patients at each institution were treated for 48 weeks with DDS, and with DDS plus nicotinamide. Tuberculin-negative patients of each group were divided in two subclasses at the outset. The patients of one subclass were vaccinated at least once, and as many as three times, with BCG; those of the other were left unvaccinated. Maximum daily dosages of drugs used were: DDS 0.2 gm.; and nicotinamide 0.5 gm. No treatment was given on Sundays.

A total of 166 patients completed 48 weeks of therapy at Central Luzon, 175 at Eversley Childs and 93 at Westfort. No evidence was found that either supplementary therapy with nicotinamide or vaccination with BCG was advantageous. Patients of all subclasses showed substantial clinical and bacteriologic improvement, but those treated only with DDS and not vaccinated showed the same progress as the others. Only 6 patients developed lepromin reactivity of the Mitsuda type, and in all of these the size of the reaction was small.

Fourth series (1957-59).—In the fourth series[8] identical double-blind experiments were carried on at two Philippine leprosaria, Central Luzon and Eversley Childs. There were four therapy groups at each institution, each with 55 patients at the outset. The drugs on trial were: (A) 4, butoxy-4′ dimethylaminodiphenyl thiourea (Ciba 1906, DPT); (B) amodiaquin (Camoquin, Parke-Davis); (C) a higher dose of DDS; and (D) a lower dose of DDS. The maximum daily dosages were: Ciba 1906, 60 mgm. per kgm. body weight; amodiaquin 0.2 gm.; higher dose of DDS 4 mgm. per kgm. body weight; and lower dose of DDS 2.5 mgm. per kgm. body weight. The therapy period was continued in this particular series for 96 weeks, except in the amodiaquin group in which the drug was discontinued at 72 weeks; most of the patients of this group were then continued on DDS. A total of 330 patients completed 96 weeks of therapy, 170 at Central Luzon and 160 at Eversley Childs.

From about the 6th to 8th week of the study, intense and persistent blueness of the skin occurred in a very high proportion of patients on amodiaquin. This blueness was especially marked in areas of infiltration. The skin discoloration was not accompanied by any other untoward signs or symptoms, and urinary findings and liver function tests did not disclose any abnormality.

At both institutions the superiority of DDS over amodiaquin was markedly evident at 72 weeks (16 patients under amodiaquin had become worse clinically as compared to only one in all the other groups), and this was confirmed at 96 weeks in spite of the fact that most of the amodiaquin patients had received DDS from the 73rd week. The thiourea compound Ciba 1906 was likewise superior to amodiaquin. In comparison with both higher and lower doses of DDS, however, Ciba 1906 showed consistently lower rates of clinical improvement at each examination, although the differences were small. Of 164 patients on sulfones, 121 or 72 per cent improved and one became worse at 96

weeks; of 77 on Ciba 1906 46 or 60 per cent improved and two became worse. The patients on the higher dosages of DDS did not improve in greater proportion than those on the lower DDS dosage, as far as could be gathered from the clinical evidence.

With regard to bacteriologic findings, judging from the reexaminations at 24 weeks and 48 weeks, no therapy was significantly better than another. By the end of 72 weeks, however, the superiority of DDS over amodiaquin was evident from both nasal and skin sites at both institutions. At 72 weeks the nasal septum sites indicated superiority of DDS over Ciba 1906, but the skin sites showed no differences; at 96 weeks this situation had not materially changed. That is, we were unable to demonstrate to our satisfaction that DDS was more effective than Ciba 1906 in reducing the bacteriologic scores for the skin sites, although DDS was more effective on the nasal sites. Ciba 1906 was more effective on the skin sites than was amodiaquin, but not on the nasal septum sites. The lower dose of DDS was found to be as effective as the higher one, on both nasal and skin sites.

Fifth series (1960-61).—Diethyl dithiolisophthalate (Etisul, ETIP), a mercaptan compound administered percutaneously, was previously reported to be very effective in leprosy but was believed to cause resistance when given alone. The fifth series was planned therefore as a controlled double-blind study of this drug as a supplement to DDS. The studies were conducted identically at two Philippine institutions, Eversley Childs and Central Luzon. There were two therapy groups at each place, each with 61 to 63 patients at the outset. The drugs used were: (A) DDS plus Etisul and (B) DDS plus a control ointment of similar odor and appearance. Patients were given a maximum daily dose of 2 mgm. per kgm. body weight of DDS, reached over an induction period of eight weeks. Beginning with the 9th week the inunctions with Etisul and the control ointment were given three times weekly, the dosage being 5 gm. per inunction. The rubbing was done on the back and maintained for a minimum of 20 minutes to insure maximum absorption. A total of 202 patients completed 56 weeks of therapy (48 weeks for Etisul) at both institutions.

No evidence was found that supplementary therapy with Etisul was superior to that with DDS alone. At 24 weeks (16 weeks for Etisul) the proportions clinically and bacteriologically improved were almost identical in the DDS plus Etisul group and the control group, and the situation did not change materially after 56 weeks of therapy with DDS and 48 weeks with Etisul. At 56 weeks clinical improvement was observed in 45.2 per cent of 104 patients on DDS plus Etisul and in 61.2 per cent of 98 patients on DDS and the control ointment, while the observed average reduction in bacteriologic scores was practically the same for the two groups.

A special study of lepra reaction was made in this series. All patients were examined weekly for erythema nodosum leprosum (ENL)

and other signs and symptoms of reaction. This complication occurred with approximately equal frequency and degree of severity in the Etisul and control groups and again was not positively associated with clinical and bacteriologic improvement at the end of the therapy period.

Sixth series (1962-63).—One of the most troublesome features of lepromatous leprosy is the repeated occurrence of reactions, generally accompanied by crops of erythematous nodules (ENL) which not infrequently become ulcerated, and often by fever and painful neuritis. The occurrence of ENL and other signs and symptoms of reaction has been noted in the clinical records of all the series. Contrary to prevalent belief, a consistent finding of the Memorial's clinical evaluation studies has been the lack of any positive association between ENL and clinical or bacteriologic improvement in the patients.

The sixth series differed from the preceding ones in that the main objective was to find a drug that would prevent or ameliorate lepra reaction during the course of therapy with DDS. Participating institutions were Eversley Childs and Central Luzon. Only new and previously untreated lepromatous patients essentially without ENL at the outset were included in the study. The drugs on trial were: Dexamethasone (Gammacorten, Ciba); Methandrostenolone (Dianabol, Ciba); and an anthranilic acid derivative (C-473, Parke-Davis). The therapy groups were: (A) DDS plus Gammacorten; (B) DDS plus Dianabol; (C) DDS plus C-473; and (D) DDS alone. Maximum daily dosages were: DDS 2.5 mgm. per kgm. body weight; Gammacorten 1.5 mgm.; Dianabol, 10 mgm.; and C-473 750 mgm. The study was a double-blind one involving the use of dummy tablets resembling each of the three drugs on trial. Treatment was carried on for 24 weeks and two consecutive batches of new patients underwent therapy at each institution. Patients were examined weekly for all possible signs and symptoms of lepra reaction and also for possible side-effects of the trial drugs.

The following conclusions were reached, based upon the records of 346 patients completing the prescribed 24 weeks of therapy at both institutions, 81 to 91 being included in each therapy group. At the dosages given in this study, none of the three trial drugs prevented or reduced lepra reaction during therapy with DDS, as far as could be judged by a comparison of person-weeks of ENL and fever in patients under DDS alone and those under DDS plus Dexamethasone, DDS plus Methandrostenolone, and DDS plus the anthranilic acid derivative. ENL was present in 25.0 per cent of the total weekly observations (for signs and symptoms of lepra reaction) in patients of the control group, compared to 31.0 per cent for the Dexamethason group, 28.5 per cent for the Dianabol group, and 37.0 per cent for the C-473 group. Clinical and bacteriologic improvement observed after 24 weeks of treatment with any of the three trial drugs was not significantly different from that observed with DDS alone.

The detailed findings of the fifth and sixth series are being prepared for publication in the *International Journal of Leprosy.*

Special Studies.—A small pilot study of Streptohydrazid (Pfizer) was carried on concurrently with the regular second series.[4] At Eversley Childs 25 patients were entered, of whom 20 completed 48 weeks treatment; and at Westfort 10, of whom 9 completed. The patients who received this therapy did no better, and no worse, either clinically or bacteriologically, than comparable patients in groups (A) (Diasone), (B) (Diasone plus INH) and (C) (DHSM plus INH) of the regular second series.

A vaccine for the treatment of leprosy had been prepared from a culture of *Mycobacterium marianum*, an acid-fast bacillus stated to have been cultivated in 1952 from a leproma by Sr. Marie-Suzanne and associates in Lyon, France. In another pilot study carried on at the Eversley Childs Sanitarium in 1956, 20 patients were each given intradermal injections of 0.1 cc. antigen marianum at monthly intervals for six injections, as a supplement to the regular treatment with DDS. Twenty-four other patients treated with DDS alone constituted a control group. Clinical improvement occurred in 70 per cent of the vaccinated patients and in 79 per cent of the control group at the end of six months of treatment. No significant bacteriologic improvement occurred in either group.[10]

The previously observed therapeutic activity of pyrazinamide (PZA) in tuberculosis and murine leprosy made it obviously desirable to test this drug in human leprosy.[6] The emergence of resistant strains in tuberculosis, however, and the good results reported with combined PZA-INH therapy suggested the advisability of using this combination in leprosy. The therapeutic value of combined therapy with PZA-INH was therefore compared with that of DDS in a 24 weeks' study. Duplicate experiments were carried out, one at Central Luzon Sanitarium and the other at Eversley Childs. Of 26 patients completing therapy with PZA and INH, 6 showed clinical improvement, 13 remained stationary and 7 became worse. Of 26 treated with DDS, 9 showed clinical improvement, 16 remained stationary and 1 became worse. No significant bacteriologic changes occurred after 24 weeks of treatment in either group at either institution.[6]

Also following a favorable preliminary report of cycloserine (CS) in the treatment of pulmonary tuberculosis, a limited trial of this drug in lepromatous leprosy was conducted in 1956 at the two Philippine institutions.[7] In two small but matched groups of patients, of whom 14 completed 48 weeks of therapy with CS (maximum dose 1.0 gm. daily) and 18 with DDS (maximum dose 0.2 gm. daily), there was no evidence of clinical or bacteriologic superiority of CS over DDS. Only 4 of 14 patients showed clinical improvement with CS compared to 14 of the 18 on DDS, although equal degrees of bacteriologic improvement occurred in both groups.[7]

CONCLUSIONS

It may be said that the Clinical Evaluation Studies of the Leonard Wood Memorial have demonstrated the practicability of adequately controlled trials in the treatment of lepromatous leprosy. It is evident, however, that these studies should be continued by the Memorial as well as by others in many parts of the world. Only if this is done will every promising drug be appraised adequately.

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