INTERNATIONAL JOURNAL OF LEPROSY
and other Mycobacterial Diseases
OFFICIAL ORGAN OF THE INTERNATIONAL LEPROSY ASSOCIATION
Publication Office: 1200 - 18th St., N.W., Washington, D. C.

VOLUME 38, NUMBER 2 APRIL-JUNE, 1970

EDITORIALS

Editorials are written by members of the Editorial Board, and occasionally by guest editorial writers at the invitation of the Editor, and opinions expressed are those of the writers.

Clinical Stages in Sulfone Treatment of Leprosy[1]

A number of drug evaluation studies on the treatment of leprosy have appeared in the literature recently, in which DDS and B.663 have been used as test drugs. Some of these were based on observation of less than 10 patients for four and one-half to six months, rapid fall of the Morphologic Index (MI) being used as the most sensitive and important criterion of effectiveness.

Marked reduction of the bacillary forms of *Mycobacterium leprae*, and corresponding increase of nonsolid elements, have been noted by those who examined the blood smears of patients receiving sulfone drugs in the past, although only a few investigators have published their findings.

Among several articles that have been published, those of Fernández and Carboni[1] in 1946, and Muir[2] in 1951, will be cited because of the easy accessibility of their articles for the ordinary worker. What appears to be chiefly responsible, however, for the current enthusiastic revival were the more recent articles of Davey[3, 4], who is recognized as a careful observer. It must be remarked in this connection that the MI has since been refined and properly quantitated.

However, there have been no published reports on changes in the solid ratio of the bacilli over a similar period of time in untreated cases. It is possible that if such reports were made, they might show that factors other than ingested drugs also can produce morphologic changes in *M. leprae*. Among such factors may be the presence or absence of factors underlying natural resistance to the disease.

1 Guest editorial.

1 FERNÁNDEZ, J. M. M. and CARBONI, E. A. The action of diasone in the treatment of leprosy (preliminary report). Internat. J. Leprosy **14** (1946) 19-29.

2 MUIR, E. Bacteriological changes under DDS treatment of leprosy. Leprosy in India 23 (1951) 116-126. *Reprinted in* Internat. J. Leprosy **19** (1951) 453-466.

3 DAVEY, T. F. Progress with new antileprosy drugs. Trans. VIIth Internat. Congr. Leprol., Tokyo (Tofu Kyokai), 1958, pp. 252-259. *Also* Internat. J. Leprosy 26 (1958) 299-304.

4 DAVEY, T. F. Some recent chemotherapeutic work in leprosy: with a discussion of some of the problems involved in chemical trials. Trans. Roy. Soc. Trop. Med. & Hyg. **54** (1960) 199-206.

Waters *et al.*[5,6], among others, have noted that the MI is low preceding erythema nodosum leprosum, and in patients showing little activity. Furthermore, the reported differences in the solid ratio among untreated patients range from very low solid counts among Filipinos[7] through an average range of from 25 per cent, as recorded by Pearson and Pettit[8] to about 54 per cent by Pettit *et al.*[9, 10, 11] reporting from Sungei Buloh, and the very high solid ratios of 90 per cent or even 99 per cent among Carville cases[12]. There appears to be an urgent need of standardizing the criteria for indentifying solid bacilli.

Shepard [13,14] made the significant discovery that experimental disease follows the injection of human leprosy bacilli into the foot pads of mice, and that the organisms in the experimental lesions multiply locally if the inoculum is appropriately diluted. Furthermore, by the use of this technic, it was determined that leprosy bacilli were killed by treatment with DDS up to 90 days, after which so few viable bacilli remained that they were barely detectable in a few specimens. Shepard *et al.*[15] also found that the infectiousness for mice decreased in the first 30 days, and was not detectable after 90 days. Another important finding was that in the range where it could be determined, the proportion of solidly staining bacilli (MI) decreased in parallel with infectiousness. Thus, it has been established that the MI and loss of infectiousness subside together within a period of three to six months.

If the MI and the test of viability of *M. leprae* in mouse foot pads give results that parallel each other closely, and since a fully equipped and specially supplied laboratory is essential for the viability tests, it would seem that the MI would serve equally well in drug evaluation studies undertaken by leprosy workers who lack access to such a laboratory.

The trial periods employed in the recent evaluation studies cited above were not long enough to permit detection of clinical changes in both control and experimental groups. More important still, such short periods do not allow sufficient time for the detection of possible cumulative toxic effects of the drug under test. Thus, there had been no clinical changes that could be ascribed to, or at least associated with, the marked rapid fall in the MI and the parallel loss of infectiousness as well. That such correlation can exist has been shown in the past in the case of sulfones, which are the only drugs that have been administered to sufficiently large numbers of lepromatous patients over long periods of years so that their true effect on host-parasite relationships with respect to parasite and host, can be traced.

In the experience of the writer, five stages may be recognized in studies of the effects of sulfone treatment of leprosy. The *first stage* has furnished spectacular clinical results, particularly because they were unex-

5 WATERS, M. F. R. and REES, R. J. W. Changes in the morphology of *Mycobacterium leprae* in patients under treatment. Internat. J. Leprosy **30** (1962) 266-277.

6 WATERS, M. F. R., REES, R. J. W. and SUTHERLAND, I. Chemotherapeutic trials in leprosy. 5. A study of methods used in clinical trials in lepromatous leprosy. Internat. J. Leprosy **35** (1967) 311-335.

7 SHEPARD, C. C., TOLENTINO, J. G. and MCRAE, D. H. The therapeutic effect of 4,4'-diacetyldiaminodiphenyl sulfone (DADDS) in leprosy. American J. Trop. Med. & Hyg. **17** (1968) 192-201.

8 PEARSON, J. M. H. and PETTIT, J. H. S. Chemotherapeutic trials in leprosy. 7. Trials of 50 mgm. DDS twice weekly in the treatment of lepromatous leprosy. Internat. J. Leprosy **37** (1969) 40-45.

9 PETTIT, J .H. S. and REES, R. J. W. Studies on sulfone resistance in leprosy. 2. Treatment with a riminophenazine derivative (B.663). Internat. J. Leprosy **34** (1966) 391-397.

10 PETTIT, J. H. S., REES, R. J. W. and RIDLEY, D. S. Chemotherapeutic trials in leprosy. 3. Pilot trial of a riminophenazine derivative, B.663, in the treatment of lepromatous leprosy. Internat. J. Leprosy **35** (1967) 25-33.

11 PETTIT, J. H. S. and REES, R. J. W. Chemotherapeutic trials in leprosy. 4. Dapsone (DDS) in low dosage in the treatment of lepromatous leprosy. A demonstration pilot study. Internat. J. Leprosy **35** (1967) 140-148.

12 HASTINGS, R. C. and TRAUTMAN, J. R. Streptomycin combined with sulfones in the treatment of relapsed lepromatous leprosy. Internat. J. Leprosy **36** (1968) 45-51.

13 SHEPARD, C. C. The experimental disease that follows the injection of human bacilli into footpads of mice. J. Exper. Med. **112** (1960) 445-454.

14 SHEPARD, C. C. Multiplication of *Mycobacterium leprae* in the foot-pad of the mouse. Internat. J. Leprosy **30** (1962) 291-306.

15 SHEPARD, C. C., LEVY, L. and FASAL, P. The death of *Mycobacterium leprae* during treatment with 4,4'-diaminodiphenylsulfone (DDS). Initial rate in patients. American J. Trop. Med. & Hyg. **17** (1968) 769-775.

pected. Even with minimal doses and irregular administration, the sulfones caused rapid drying-up of the multiple body ulcers suffered by most of the moderately affected and advanced lepromatous patients in the presulfone era. The dressing of these ulcers constituted the heaviest and most expensive part of the medical care of the patients and required establishment of ulcer clinics in every leprosarium. Even in ordinary wards nursing aides spent half their time dressing these ulcers. Not affected were trophic plantar ulcers and the superficial ulcerations produced by severe ENL.

The most striking result, however, was not the healing of the ulcers, which may have been brought about by an antibiotic effect the sulfones may have had on secondary invaders, but rather the disappearance of the indurated areas of infiltration that produced the deepest and most recalcitrant of the ulcers. What particularly attracted widespread attention was the large savings in gauze, cotton-wool, and dressings, which led many to hail the new treatment as by a "wonder drug."

Similarly, no word could better describe the results of laboratory experiments on 90-day DDS treatment of mouse foot pad lesions, if they can be projected to indicate that such treatment will render bacilli-laden lepromatous cases noninfectious. If this result is confirmed by field studies similar to those that established the infectiousness of such cases in terms of incidence rates[16], then eradication of leprosy may be expected in many countries within a few years, since most of their lepromatous cases appear to have already received at least the 90-day sulfone treatment, if we are to judge from their low MI's.

The process of rapid healing of skin ulcers extended to those involving the larynx, which produced the characteristic hoarse voice of advanced cases. This result provided better pin-pointing of the onset of the effects of the drug. Following a few injections of promin administered irregularly, an improvement revealed partial healing of the ulcers, with complete restitution of diseased tissue in a few more months. This effect of the drug has made it unnecessary to perform the life-saving emergency tracheotomies so frequently required in the presulfone period.

Even though examination of smears for the MI was not made at the Tala Sanitarium at the time, it is reasonable to assume that the quick clinical response noted was associated with a rapid fall in the MI, and presumably also with loss of infectiousness of the organism.

Equally impressive, but noted only somewhat later, was the prevention of leprotic involvement of the eyeball, the most common cause of blindness in leprosy.

This initial stage in the course of sulfone treatment of leprosy lasts about one year. Since established lesions of the disease, such as infiltrations, and bacteriologic findings remained unaffected, however, these effects of the drug in early stages of the disease should be regarded more as amelioration of prominent symptoms rather than as arrest or cure of the leprosy.

The next (*second*) stage turned out to be less spectacular, but also significant in that it established the fact that sulfones can reverse the bacteriologic findings and clear up clinically active lesions, although at a much slower pace than the drying-up of ulcers. This second stage would correspond to the period of "bacteriologic clearance" of the invading organism; i.e., not only had the *M. leprae* been killed off completely, but their "cadavers" and parts thereof had not been effectively "buried" or otherwise disposed of by the host.

The Bacillary Index (BI), which serves as a measuring stick for this period, may show definite improvement of some of the smears after two years, but complete bacterial negativation of *all* the skin and nasal smears takes considerably more time.

In a rapid survey conducted last year among patients admitted to the Eversley Childs Sanitarium as moderately advanced lepromatous cases, about 80 per cent had become clinically and bacteriologically negative after seven years of supervised treatment with standard doses of 600 mgm. of DDS per week. This period may be taken

[16] DOULL, J.A., GUINTO, R. S., RODRIGUEZ, J.N. and BANCROFT, H. The incidence of leprosy in Cordova and Talisay, Cebu, P. I. Internat. J. Leprosy **10** (1942) 107-130.

as the average duration of the second stage. Some leprosy workers have tried to effect a short-cut to this exasperatingly long period by disregarding a few slightly positive skin and nasal smears, but this practice usually results in worsening of the leprosy in later years.

The *third stage* is a period of apparent arrest of the disease, which may be attributed to the sulfone treatment. It is not possible to determine how long this period lasts in each case, since most patients involved try their best for obvious reasons to mix with the general population, so that they can no longer be traced, but in a group of 30 specially studied cases that had relapsed, this period lasted from two to 12 years, with an average of seven years.

The best measure of the real effectiveness of any drug treatment in such a chronic infectious disease as leprosy is, of course, the number of cases that relapse. No drug can be considered as an effective treatment if all that it accomplishes is temporary improvement in the disease process.

Clinical and bacteriologic return of the disease, or its relapse after a period of quiescence, corresponds to the *fourth stage* in the course of leprosy which may be ascribed to the effects of sulfone treatment.

Quagliato, Bechelli and Marquez[17] have recently reported an average accumulated relapse rate of 11.4 per cent at the end of five years among patients who had received regular treatment, while 22.7 per cent reactivations took place in patients who had received regular treatment for the longer period of 10 or more years. On the other hand, among those receiving irregular treatment for 10 or more years (as may be expected among patients served by the traveling clinics employed in most countries), the accumulated percentage of reactivation rose to the alarming average of 57.0 per cent. This indicated the importance of well supervised administration of a drug given by mouth.

17 QUAGLIATO, R., BECHELLI, L. M. and MARQUES, R. M. Bacteriological negativity and reactivation of lepromatous patients under sulfone treatment. Presented at Ninth International Leprosy Congress, London, 1968. *Abstract in* Internat. J. Leprosy **38** (1968) 655-656.

Recently the writer examined a small group of healthy-looking ex-patients who had been rendered "negative" by sulfones for 12 or more years. Most of them showed various degrees of scarring from previous bouts of severe ENL accompanied by extensive ulcerations, and some exhibited contracture of the fingers, but the disease appeared to have been arrested by the treatment and had been spared by it from proceeding to the last lap of the true "burnt-out" stage. In other words, such cases belong to the *fifth* and final period of sulfone therapy.

Thus, we have traced over a period of 25 years the impact of sulfones on the progress of human lepromatous leprosy.

The survey here described shows that sulfones do have a positive effect on the course of lepromatous leprosy by deviating and even interrupting it for long periods of time in most cases. It shows also that these changes go hand-in-hand with variations in the behavior of the *M. leprae*. This fact may suggest to some students that perhaps there are still unrecognized phases in the life-cycle of pathogenic acid-fast organism, which develop under long-continued stress caused by exposure to an active drug.

In summary it may be said that present drug evaluation studies based on a few patients, and conducted over a period of weeks or months instead of years, have proved valid by indicating whether or not a tested drug is active against the leprosy bacillus. However, as already mentioned, in the short periods currently followed, it will not be possible to determine the ultimate effect on patients. Great care must be taken to ensure that the patients selected for trial are free from any other organic diseases, and laboratory examinations must be made frequently so that possible injuries to important organs may be detected before they become irreversible.

It is suggested that DDS drug trials should include at least 20 patients in experimental and another 20 in control groups, and should be continued for two years unless there is evidence of toxicity or progression of the disease.

Market sale of drugs cleared favorably through such trials should be permitted so

that patients and governments faced with the problem of endemic leprosy can benefit from their use.

Short-term trials should be considered as screening devices rather than true tests of the effectiveness of a new antileprosy drug. The latter can be determined only by extended trial including the observation of numerous patients over a period of several years.

Leonard Wood Memorial
Cebu Skin Clinic
Cebu City, Cebu, Philippines

If a final lesson, derived from the experiences cited above, may be added, it is that one cannot "extrapolate" the clinical and laboratory findings of lepromatous cases observed for a few months only, or data obtained from experimental models using short-lived animals, to the long and variable course measured in decades through which this type of leprosy passes to the end of the infection.

—Jose N. Rodriguez, M.D., M.P.H.