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EDITORIALS

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Controlled Trials in the Chemotherapy of Leprosy

This issue of THE JOURNAL carries the fifth of a series of papers published recently by Waters, Pettit, Rees, Ridley and Sutherland under the general title "Chemotherapeutic trials in leprosy." The major objective of the series has been to develop procedures for precise evaluation of the results of treatment with any drug selected for investigation in leprosy. The series had its origins in studies of drug therapy initiated in patients at the Sungei Buloh Leprosarium, Malaysia, ten years ago. From the outset emphasis has been laid on the need for scientific control in clinical appraisal of any specific drug therapy, and methods to be used to ensure adequacy of that control.

The procedures under study were outlined by Waters, Rees and Sutherland at the VIIIth International Congress of Leprology in Rio de Janeiro in September 1963 (1). Indeed the wording of that initial exposition of aims and procedures and the description in the mature compilation reported in this issue of THE JOURNAL, testify to a steadfastness in purpose and method throughout the series. Article No. 1 of the series represented a clinical experiment, well controlled in design and course, in which a comparison was made of the results of treatment with DDS alone and DDS plus Macrocyclon in matched pairs and otherwise selected patients with lepromatous or near-lepromatous leprosy (2). Subsequent papers have dealt wth a corresponding comparison of DDS alone and DDS plus ditophal (Etisul) (3), a pilot trial of the effect of the riminophenazine

[1]WATERS, M. F. R., REES, R. J. W. and SUTHERLAND, I. A study of methods used in controlled chemotherapeutic trials in lepromatous leprosy. Presented at VIIIth Internat. Congr. Leprol., Rio de Janeiro, September 1963. *Abstract in* Internat. J. Leprosy **34** (1963) 550-551.

[2]WATERS, M. F. R. Chemotherapeutic trials in leprosy. 1. Comparative trial of Macrocyclon plus dapsone and dapsone alone in the treatment of lepromatous leprosy. Leprosy Rev. **34** (1963) 173-192.

[3]WATERS, M. F. R. and PETTIT, J. H. S. Chemotherapeutic trials in leprosy. 2. Comparative trial of dapsone plus ditophal (Etisul) and dapsone alone in the treatment of lepromatous leprosy. Internat. J. Leprosy **33** (1965) 280-296.

derivative B.663 on lepromatous leprosy ([4]), DDS in low dosage in the treatment of lepromatous leprosy ([5]) and, finally, a closing retrospective study of methods used in clinical trials in lepromatous leprosy, i. e., the fifth study in the series, carried in this issue of THE JOURNAL ([6]). In the fifth paper the authors have extracted from previous experience in the other studies certain facts enabling them to set forth generalizations on such vital matters as (1) the type of patient required for such a study, (2) methods to be employed in assessing clinical progress, including pertinent bacteriologic and histopathologic tests, as well as clinical observations, (3) the number of patients practical for the desired assessment, (4) random allocation of patients to the different treatment series, including the elements of stratification by age or other groups and matching of pairs, and finally (5) a suitable type of statistical analysis of results, designed to obviate some of the difficulties involved in setting up appropriate matched pairs.

In the matter of selection of patients the authors reached the firm conclusion that previously untreated "polar" or "pure" (L2 and L3) lepromatous leprosy patients formed the best group for chemotherapeutic trials, representing, on the one hand, the well defined target of a pathologically active process, and, on the other, a group more nearly homogeneous than could otherwise be selected. It is noteworthy that when this factor was established as a requisite in the selection of patients, differences within the trial groups with respect to sex, age, race and duration of disease i.e., factors generally considered as vital in systems of matching of pairs, actually proved of less importance than the factor of clinical severity of the disease.

Among the methods of assessment to be used, various types of clinical evaluation were studied, including (1) that of technically "blind" conduct of the trial, so as to obviate bias, in which an independent assessor graded degrees of improvement or deterioration, (2) laboratory assessments, among which the morphologic index (MI), measuring the percentage of solid-staining bacilli in diagnostic smears, was accorded special importance, and (3) suitable statistical analysis, in which elements believed to be of original prognostic importance for each patient were incorporated in the analysis of difference in response between two treatment series (i.e., the technic for analysis of covariance).

The above is but a sketchy outline of the principles set forth by the authors named for suitable assessment of the value of any procedure of chemotherapy for leprosy. It is noteworthy that the studies were of one method of treatment as compared with another, rather than the rigorous one of comparison of the results of a given procedure of chemotherapy with the course of leprosy in patients to whom a placebo was administered instead of the drug on trial. It may well be that the latter type of comparison is no longer practical or admissible. In this connection the reader is referred to a retrospective analysis by Levy and Murray in the *Correspondence* section of this issue of THE JOURNAL (393-394).

The authors of the series here described called attention to one readily understandable difficulty in making an adequate trial by the procedures proposed, viz., the decreasing supply of untreated pure lepromatous patients available for such a study. In the light of this fact they suggest the value of short term "pilot trials" of relatively brief duration on a limited number of patients, in which special emphasis is placed on the speed of fall of the morphologic index in the course of treatment. Results to date suggest that as few as six patients and as short a duration of study as four and a half months may be sufficient for such a pilot trial. In those cases in which the results of a pilot trial so conducted appeared favor-

[4] 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.

[5] 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 trial. Internat. J Leprosy **35** (1967) 140-148.

[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.

able, a larger and longer definitive trial, using the various methods of clinical evaluation here described, could be made. A detailed protocol for the conduct of a pilot trial is given in the fourth paper of the series ([5]).

In the fifth paper of the series, printed in this issue of THE JOURNAL, frequent reference is made to the "Clinical evaluation studies in lepromatous leprosy" made by the Leonard Wood Memorial, which were started some fifteen years ago and have been reported periodically in a series of publications since that date ([7, 8, 9, 10, 11, 12]). In the first series report, J. A. Doull ([7]) pointed out the need, urgent at the time, for critical evaluation of drugs used in the treatment of leprosy, and noted the rapid adoption of the sulfones in practice, reflecting an already widespread view among leprologists that the sulfones were superior to all other drugs, including chaulmoogra oil, in the treatment of leprosy. He stressed the fact, however, that the "popularity of (the sulfone) drugs at times exceeded their established therapeutic value," and noted a genuine lack, up to the time, of sound pharmacologic support that could come only from studies accurately controlled, including an adequate number of patients for validity of results. The initial study of the Leonard Wood Memorial series ([7]) represented an international effort, in which strict protocols were established for clinical appraisal of patients' progress and objective evaluation of results.

Some account of the results of these studies is given in the history of the Leonard Wood Memorial, constituting Part 2 of the preceding issue of THE JOURNAL. For present purposes it may be noted that in the first series reported, in which five drugs were tested, and a placebo group was employed as a control in two locations of the study, significant results were secured indicating the value of two sulfones, viz., Diasone and DDS, and dihydrostreptomycin. This was at a time when laboratory refinements in assessment, such as the morphologic index, were not yet in practice, but special emphasis was laid at the time on the achievement of bacteriologic negativity in skin smears. Subsequent studies, the last of which was published in the preceding issue of THE JOURNAL, have illustrated a growth in technics for appraisal of results. In this study, conducted as a "double-blind" investigation in duplicate in two Philippine leprosaria, some 350 patients were divided into four matched groups treated for 24 weeks. The study represented a noteworthy sharpening of standards in the interim since the first of the six series, in the evaluation of results.

The lengthy investigations to which attention is drawn in this editorial have pointed up the exhaustive detail in procedure and analysis, as well as objective methods used to prevent bias, that are considered today as essential in meeting current research standards. While an inescapable mandate is recognized, placed by modern science on the element of scientific control, it is a little disconcerting to recall that some of the most notable achievements

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[7] DOULL, J. A. Clinical evaluation studies in lepromatous leprosy. First series: Diasone (Diamidin), 4,4'-diaminodiphenyl sulfone, dihydrostreptomycin. Internat. J. Leprosy **22** (1954) 377-402.

[8] DOULL, J. A., RODRIGUEZ, J. N., DAVISON, A. R., TOLENTINO, J. G. and FERNANDEZ, J. V. Clinical evaluation studies in lepromatous leprosy. Second series: isoniazid and Diasone (Diamidin), isoniazid and dihydrostreptomycin. Also a pilot study with streptohydrazid. Internat. J. Leprosy **25** (1957) 173-192.

[9] DOULL, J. A., RODRIGUEZ, J. N., DAVISON, A. R., TOLENTINO, J. G. and FERNANDEZ, J. V. Clinical evaluation studies in lepromatous leprosy. Third series: nicotinamide, and BCG vaccination as supplements to diaminodiphenyl sulfone (DDS). Internat. J. Leprosy **26** (1958) 219-235.

[10] DOULL, J. A., RODRIGUEZ, J. N., TOLENTINO, J. G., FERNANDEZ, J. V., GUINTO, R. S., RIVERA, J. N. and MABALAY, M. C. Clinical evaluation studies in lepromatous leprosy. Fourth series: 4,butoxy-4'dimethylaminodiphenyl thiourea (DPT), amodiaquin, and 4,4'-diaminodiphenyl sulfone (DDS) 2.5 mgm. and 4 mgm. per kgm. of body weight. Internat. J. Leprosy **29** (1961) 291-317.

[11] DOULL, J. A., TOLENTINO, J. G., RODRIGUEZ, J. N., GUINTO, R. S., RIVERA, J. N., FERNANDEZ, J. V. and MABALAY, M. C. Clinical evaluation studies in lepromatous leprosy. Fifth series: diethyl dithiolisophthalate (Etisul) as a supplement to 4-4'-diaminodiphenyl sulfone (DDS). Internat. J. Leprosy **33** (1965) 186-205.

[12] DOULL, J. A., TOLENTINO, J. G., GUINTO, R. S., RODRIGUEZ, J. N., LEANO, L. M., FERNANDEZ, J. V., RIVERA, J. N. and FAJARDO, T. T. Clinical evaluation studies in lepromatous leprosy. Sixth series: effect (on lepra reaction) of supplementing DDS with dexamethasone, methandrostenolone, or mefenamic acid. Internat. J. Leprosy **35** (1967) 128-139.

in preventive therapy and drug treatment were first made without benefit of scientific control. One thinks at once of cowpox vaccination against smallpox and the use of quinine to prevent or cure malaria. Indeed much more recent accomplishments of the same nature could be cited. The use of streptomycin and isoniazid in tuberculosis is a case in point. Initial recognition of their value was based on clinical observation, without what would now be considered adequate statistical control. To be sure, an abundance of controlled studies came later. But the first observations were simply of spectacular clearing of lesions as seen in x-ray films in patients whose course had hitherto been slow and doubtful or even one of deterioration. Those who attended tuberculosis clinics in the early days of use of these drugs will recall how startling was the improvement as compared with the slow and discouraging course in patients of the same type for many years past.

Indeed something similar can be said of leprosy. Binford has called special attention ([13]) to the complete lack of what is now considered indispensable control in the first studies demonstrating the value of the substituted sulfone Promin. ([14]) The original classic on this subject presented summaries of progress in 22 patients who had completed at least 12 months of Promin treatment. In most of the cases the course of the patient was remarkably favorable. It will be noted, however, that a sense of inadequacy in this respect was recognized by the authors themselves. In the same paper a second study is recorded briefly, of a Promin-like drug socalled Internal Antiseptic 307 (sodium-4,4'-diaminodiphenylsulfone-2-acetylsulfonamide) which was given to one selected group of patients, while a second group, untreated except for a simple placebo, was set up for control. The former did better than the latter. The controlled trial is now largely forgotten. What is remembered is the uncontrolled investigation of Promin. As the authors said, in all simplicity, "Promin can be considered to have opened a new avenue in the chemotherapy of mycobacterial diseases."

These few remarks on the advent of Promin naturally will not be taken as derogatory to the principle of scientific control in determining the value of a medicament for disease. Such control is indispensable in clinical or experimental evaluation. They are made only because chance, too, is sometimes helpful. In the future, as in the past, first observations on something that ultimately proves invaluable may be ushered in without the backing of any formulated study. Repetition becomes tiresome, perhaps, but Pasteur's old adage of "chance and the prepared mind" is not to be forgotten.

—E. R. Long

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[13]Symposium on Sulfones. U.S.-Japan Cooperative Medical Science Program. San Francisco, 11 May 1967.

[14]Faget, G. H., Pogge, R. S., Johansen, F. A., Dinan, J. F., Prejean, B. M. anl Eccles, C. G. The Promin treatment of leprosy. A progress report. Publ. Hlth. Rep. **58** (1943) 1729-1741. *Reprinted in* Internat. J. Leprosy **34** (1966) 298-310.