Interpretation of Published Papers on Controlled Clinical Trials

TO THE EDITOR:

Although the major (international) leprosy journals subject all research papers submitted to their editors to careful peer review, it still behooves leprologists to read critically those that are published. This is especially true for all clinical trial papers, whether dealing with the chemotherapy of leprosy or the treatment of reactions. There are a number of good reasons, including the following: a) Some papers may not be scientifically quite satisfactory, yet they contain important data, so that their findings warrant checking by others using correct methodology. The responsibility borne by the referees and, ultimately, by the editor for publishing such communications is considerable. b) The editor and referees may consider that a strongly held heterodox view should be published so that the scientific world may study the evidence (or lack of it) in its favor. c) The editor and referees may be subject to current bias and not recognize

the weakness of an argument. (One recalls the conviction in the 1960s and 1970s that the dose of dapsone influenced the incidence of erythema nodosum leprosum [ENL].)

Readers of clinical trials should always note:

The source of the patients. For example, in general the average severity of tuberculoid leprosy is greater in hospital than in field patients. Although the bulk of tuberculoid patients are treated in the field, most clinical trial reports are received from hospital settings.

A full 10% "failure rate" among severe borderline tuberculoid (BT) hospital patients might well represent a less than 1% failure rate among field tuberculoid or paucibacillary (PB) leprosy patients. The differences may be even greater for field areas using active case findings on a larger scale.

The allocation of the patients. Normally, this should be by a completely random method to exclude bias. Sometimes in large field trials it may be necessary, for operational reasons, to allocate patients to drug regimens by village or district. In these circumstances, it is essential that the several districts should all be handled alike. In hospital trials, one regimen may require a period of hospital admission, and another be performed on an outpatient basis. In these circumstances, patients who refuse hospital admission should not be allocated to the outpatient regimen(s), since the willingness or refusal to stay in hospital may in part be related to particular clinical or social problems.

In trials of reactions, it is important to stratify (allocate and analyze separately) treated and untreated patients, if both groups are being admitted. It should be remembered that most, although not all, reversal reactions commence in BT leprosy within the first few months of treatment (and in a minority in untreated patients); whereas in borderline lepromatous (BL) patients many, not all, occur within the first year of treatment. If an intake consists of multibacillary (MB) leprosy patients of varying and undefined periods of treatment, with no stratification, it is possible that, by chance, most of the BL patients treated for more than 1 year may be allocated to one group, with most treated for less than 1 year allocated to another group, thereby producing a difference in the incidence of reversal reactions between the two groups.

The handling of the patients during and after the trial. It is important that the patients in each treatment group should have their appointments, examinations, investigations, etc., carried out in identical ways. For example, patients being treated for different periods of time, whether PB or MB, should all be handled in the same way after the first group has stopped treatment and while the other group(s) remain on chemotherapy.

Whether patient assessments are performed "blind." Wherever possible, assessments, including clinical assessments, should be performed "blind." Histological assessment is therefore particularly helpful, especially if the independent histological assessor is working in another center or country. Smears should also be examined blind by coding the slides.

But the reader should not place too high a reliance on the term "blind," and even less on "double blind." Most drug regimens are distinctive. Patients, for example, in ENL trials can easily distinguish thalidomide from placebo because of the soporific effect of the former. In chemotherapy trials, many patients can equally well distinguish the thioamide drugs from placebo by their effect on taste and by their gastrointestinal side effects.

In brief, a healthy critical approach is essential.

The subject is covered very well in general terms, but without reference to leprosy, in "How to Read a Clinical Journal," Part 3, Chapter 12 of *Clinical Epidemiology* by Sackett, Haines and Tugwell (Boston and Toronto: Little Brown and Co., 1985).

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