LETTERS TO THE EDITOR

Nigeria Leprosy Service Research Unit,
Uzuakoli,
E. Nigeria.
17th March, 1956.

The Editor,
Leprosy Review,
London.

Sir,

The continued appearance of new drugs having anti-tuberculous activity makes your editorial in the October 1955 number of the LEPROSY REVIEW on the subject of their testing in leprosy as timely as it is valuable. Some experience in this type of work prompts me to offer a personal opinion on some of the theoretical and practical aspects of it.

It does not follow that because a drug has been used with safety in the short term treatment of tuberculosis that it is equally suitable for leprosy patients. A case has already arisen where dangerous toxic effects appeared in tuberculous patients in the fourth month of treatment, and the long term treatment inevitable in leprosy may involve a situation not covered by the toxicity tests undertaken by the manufacturers before issuing the drug. It follows, (a) that initial trials demand in the interests of the patient volunteers concerned, a very reliable laboratory service making it possible to maintain a close watch on red and white blood cell formation, liver and kidney function, and (b) that several months must elapse before reliable evidence can be forthcoming as to the suitability of a drug on toxicity grounds.

The number of centres suitable for such primary trials is limited. It would appear desirable to initiate trials at two or three of these simultaneously, recognising from the start that if the drug is found active, long term trials are involved in each case. A comparison of findings after six to nine months, if establishing the facts of anti-bacterial activity and low toxicity, could then lead to additional trials at centres less fully equipped.

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Choice of patients. I am not at all sure that the first patients chosen for such trials should be advanced lepromatous cases. Patients of this type who have had no previous treatment are becoming increasingly uncommon, and when found, their physical

condition often renders them unacceptable for trial purposes. Furthermore, at least six months trial may be needed before convincing evidence of drug activity may be forthcoming in such patients. As encountered here they are usually in urgent need of treatment, and deserve the best available, namely sulphones, without delaying for some months while taking a drug which is at best an unknown quantity.

Early lepromatous cases are in a different category, applying the term " early " to mean " of short duration." Such patients are usually able-bodied, suffering as yet very little disability as the result of their infection, yet often harbouring considerable numbers of bacilli in their skin. Their response to sulphone treatment is usually rapid, both clinical and bacteriological improvement being unmistakable in six months or less, and if placed on a new drug would thus not need a longer period than this for a judgment on its activity to be made.

Furthermore, active tuberculoid and indeterminate cases are not to be despised. The disease is a unity, and if a drug has activity against *M. Leprae*, all forms of the disease harbouring living bacilli will respond to it. We have not encountered, nor are we likely to encounter, a drug active in one form of leprosy and inactive in another. Tuberculoid cases can yield rapid information. Under sulphone treatment the vast majority show signs of resolution within three months. Resolution of such cases in the absence of treatment is of course common enough, though it is extremely unlikely that a group would all do this simultaneously. Even if it is conceded that the resolution of such cases is of little statistical value, their failure as a group to show resolution is quite a different matter, and is indeed definite and valuable positive evidence that the drug concerned is of low activity in the dosage tested. If forthcoming at all, such evidence will be obtained within three months of starting the trial.

It is therefore a sound procedure to build up a trial group of patients on a basis of early lepromatous and active tuberculoid cases in the first instance, adding suitable more advanced lepromatous cases as signs of drug activity begin to appear, up to a total of 16 to 20 lepromatous cases and 8 to 10 tuberculoids. With such a group six months suffices for proof of activity, and twelve months for a short term comparison between the drug concerned and DDS. A group of this size is necessary if allowance is to be made for wastage, individual idiosyncrasy, and other incidents, and manufacturers should recognise this.

Such a method of selection is in accord with practical necessity.

Nowadays one rarely encounters an adequate group of previously untreated suitable patients, capable of being placed simultaneously on a new drug. Patients have to be selected as they come, today a lepromatous patient, tomorrow a tuberculoid patient, and, allowing for controls, it inevitably takes time to build up a group of trial patients of adequate size. We therefore very definitely need to include patients of those types which are going to yield an answer as quickly as possible as to the suitability of the drug for wider trials.

It is worth stressing the importance of the word "suitable" where these patients are concerned. The successes of sulphone treatment introduce an important ethical aspect into the matter. Reference has already been made to this where severe lepromatous patients are concerned. It applies in fact to others as well. As a general principle we are not justified in accepting for pilot trials any patient whose deprivation of sulphone treatment for three to six months can be considered detrimental to his subsequent progress. This eliminates all patients with signs of active neuritis of motor nerves, ulceration of the nose or larynx, or involvement of the eyes in any way. Suitability must also depend on the existence of a clear clinical picture of active disease, classification being supported where necessary by biopsy.

Controls. The selection of controls is also not without its difficulties. The adoption of individual controls, patient for patient, is certainly to be advocated, but the difficulties and limitations of this system need recognition. In the first place, the patient and his control must be strictly comparable. In addition to type, degree, and duration of the disease I would add sex, approximate age, and also equality in lepromin reaction. This last item is important, for differences here may influence progress quite considerably. Even though 90% of lepromatous patients may be steadfastly lepromin negative, the remaining unstable 10% may be a source of real difficulty. These additional factors narrow down very considerably the choice of suitable controls, so that a rather large reservoir of patients on sulphone treatment is necessary to provide what is needed.

As a trial proceeds, this system of controls leads to other difficulties. There is first the problem of wastage. If a control patient drops out from observation for one reason or another, the corresponding trial patient may also be wasted. Furthermore, over the long period needed for a full clinical trial, sufficient individual variation in progress remains between one leprosy patient and another to rob individual controls of much of their value. For short term assessments it may be concluded that individual controls are valuable, but in long term studies it is probably more accurate to review the progress of each type of patient as a group, in comparison

with groups of the same type of patient receiving DDS.

Perhaps after all the best yardstick of progress in patients receiving new drugs is that provided by the accumulated experience of DDS treatment at the centre concerned. We have now available, in the records of DDS treatment, ample material for a general statement of progress relating to each type of leprosy during the first and subsequent years, and this, based on large numbers, is probably more accurate than the findings in a small group could possibly be.

I have found the preparation of such a statement by the analysis of records here a salutary experience, reminding me that the achievements of DDS are out of all proportion to its deficiencies. It is right therefore as you say, that the conditions for testing new drugs should be stringent. Only by making them so will trials of new drugs really be to the advantage of present and future patients.

I remain,

Yours faithfully,

T. F. DAVEY, M.Sc., M.D.

[Further comment on this very important subject will be welcomed from those who like Dr. Davey have had practical experience of controlled trials of drugs, especially drugs for the treatment of leprosy.—EDITOR].

Dear Sir,

In perusing the October number of the REVIEW (which has just reached me) I observe that you have inserted a report of mine on leprosy. Although I am gratified that you considered the standard of the work as one meriting publication, there are a number of hiati on which I should ask the indulgence of your readers.

The first is that since having had the benefit of Dr. Cochrane's opinion on what should be done out here, my concepts of leprosy control as is implied in the word " segregation " has been basically altered.

The second point I have to make is that for anyone other than those who have an inside knowledge of the operation out here, the position must be obscure. That is to say, while rehabilitation is being handled by an Agency of the United Nations (United Nations Korean Rehabilitation Agency or in short UNKRA) disease control was at the time that the report was made, the responsibility of the American Army embodied in the Korean Civil Assistance Command (KCAC). The last mentioned was in effect an advisory group using professional staff who were (like myself) mostly on loan from UNKRA, or recruited as Department of the Army Civilians. My role was therefore one of an adviser with a special responsibility for the Prevention of Epidemic Disease. Leprosy

merely came into my field as a study and it was not the subject of an army sponsored programme of control.

I have also mentioned " AFAK," or in clear, Armed Forces Aid to Korea.

The intention of this plan was to supplement what had already been achieved in the reconstruction of the country by the building of churches, orphanages, schools, hospitals, etc., and its secondary objective was to give an interest to the men of the American Army who found themselves in danger of being bored in an eastern country devoid of the ordinary amenities. The men themselves were responsible for the supervision of such work.

Abbreviations used in my report were in common useage out here, but unless the background is understood, they may well be unintelligible!

Yours faithfully,

(Dr.) M. L. SMITH.

U.N.K.R.A.,
Korea.
4th January, 1956.

Dear Sir,

With reference to the second part of my contribution entitled " Leprosy in Korea," which you have kindly published in the January issue of LEPROSY REVIEW, there is an error on page 19, line 16 from the top. The sentence reads " In our study of child leprosy in India we found that 7% of childhood leprosy . . . etc., etc." The figure should be 70%. This was an error which was in the original mimeographed report, and an errata slip was unfortunately omitted.

Since the publication of these figures the follow up work at the Children's Clinic at Saidapet has continued, but we have, as yet, no evidence to refute the contention that much child leprosy is benign, and that the lesions disappear before adult life is reached. You yourself, Sir, many years ago, pointed out that leprosy was a self-healing disease. The problem, therefore, is not the amount of leprosy in the community, but what is of importance is the percentage of cases that develop into the more serious forms of leprosy, either from the point of view of becoming open cases or resulting in deformity. In countries where leprosy is an endemic disease it would be well to study its natural evolution, so that our treatment and preventive measures may be applied with more enlightened knowledge.

I am,

Yours truly,

R. G. COCHRANE, M.D.