EDITORIALS

ARE WE SATISFIED WITH SULPHONES FOR THE TREATMENT OF LEPROSY?

It is agreed by all with practical experience of the treatment of leprosy that a revolutionary change has taken place in the last ten years, both for the patient in his hope of recovery and for the endemic area in the hope of control.

This is chiefly the result of the discovery of the effects of sulphones on leprosy, first in the more complex expensive derivatives of diaminodiphenylsulphone, and more recently in the simple and economical parent substance, DDS. Now that the rules of its use have been standardised, DDS (whether given orally in tablets or by injection of the suspension) has been accepted almost universally as the treatment of choice.

DDS has certain drawbacks. Lepra reaction occurs, and in some patients, even in spite of very gradual initiation from minute doses, painful reactions with generalised febrile symptoms intervene during the earlier months, and occasionally continue for long periods. Also in a small minority there are toxic symptoms such as dermatitis, which, however, can generally be easily controlled.

The chief defect, however, is the long period required to render the patient bacteriologically negative, sometimes extending in advanced lepromatous cases to as much as ten years or more. Yet, when one considers the amount of leproma that has to be got rid of, is this any wonder? As Dr. Wade[1] has said: " When the large—even tremendous—numbers of bacilli that are often present per field in smears of tissue pulp from lepromas are considered, some degree of appreciation can be gained of the myriads of them that the patient must get rid of in recovering from lepromatous leprosy. Hanks once estimated that the numbers average 2.5 billion—two thousand five hundred millions—per milligram of leproma tissue."

Still, to those of us who fought against leprosy in the old days with no better drug than chaulmoogra oil, the advantages far more than outweigh the defects. Let us recount the more important of these advantages:—

(a) The rapid healing of lepromatous ulcers of the skin and mucous membranes, bringing comfort to the patient and rendering him less infectious.

(b) The flattening of nodules and other swollen leproma, causing marked improvement of clinical appearance.

(c) The assurance that, slow as the improvement may be, it will go on towards ultimate recovery.

(d) In patients where an early diagnosis is made before they become infective, the assurance that the disease will not advance but get gradually better; and that, with the simplest form of treatment, he may continue his work without need of isolation.

(e) After use of sulphones up to eleven years the writer's experience, which is confirmed by that of many others, is that there is no clear evidence of drug resistance, however long the treatment has to be continued. This is one of the most remarkable features of the sulphones in leprosy, when we compare the drug resistance so common in recent remedies for tuberculosis. According to Scadding[2] the sort of tuberculosis most favourable to the emergence of resistant strains is " acute rapidly progressive disease, with extensive caseation and cavitation. It is probable that the danger of the emergence of resistant strains from less extensive and active lesions is considerably less." One might argue from this that the advanced lepromatous case, with its myriads of bacilli, and the need for treatment for many years, would be the kind of case to develop drug-resistant strains if they could develop at all; and that the absence of evidence of resistance to sulphones indicates that M. leprae, from its very nature and its inability to grow except in human tissues, cannot form mutants. But on the other hand, improvement of leprosy under thiosemicarbazone is found to cease after a few months, suggesting that in this instance drug resistance does develop. If these suggestions are correct then absence of drug resistance appears to be a special feature in the relationship between M. leprae and sulphones.

To sum up, we have in the sulphones, and particularly in DDS, despite certain defects, a most valuable instrument for the cure and control of leprosy. In certain countries there is evidence that, as the result of mass treatment with sulphones, leprosy is beginning to be brought under control. In fact the main obstacles to bringing about control are not the defects of sulphones but the scarcity of proper staff and of finance, and often the absence of efficient organisation.

These essentials being difficult to obtain, we naturally look forward to finding other drugs which will show the advantages of sulphones without its defects. How are we to set about finding such drugs?

(1) Wade, H.W. Internat. J. Lep., 1954, 22, p. 347-8.
(2) Scadding, J. G. Lancet, July 16, 1955, p. 100.

DEVELOPMENTS IN MYCOBACTERIAL RESEARCH

Leprosy research has certain handicaps compared with research in other diseases. One of these is failure to cultivate Myco. leprae outside the tissues of the human body. Another is the small degree of interest that has been taken in leprosy research, and the smallness of the number of suitable workers that it attracts.

This latter handicap shows signs of amendment as evidenced by a meeting recently called in London by the Colonial Medical Research Committee, when twenty-two research workers met round a table and discussed ways and means for the co-ordination of leprosy research in the U.K. and the Commonwealth. Such an occurrence could not have been envisaged a few years ago.

The chief reason for this rising interest in leprosy is a kind of cross-fertilisation between research in tuberculosis and leprosy, and new attention to the whole field of mycobacteria.

The use of sulphones in leprosy was suggested by their effects in experimental tuberculosis, though they proved of little value in clinical tuberculosis. Streptomycin, isoniazid and PAS, useful in clinical tuberculosis, are of little use in leprosy. Isoniazid and streptomycin are more useful than DDS in control of rat leprosy in rats. These and similar findings suggest considerable possibilities for useful research into the basic action of these drugs and the reasons for these differences.

Another line of mycobacterial investigation is that by Hanks into the metabolism and viability of Myco. lepraemurium. By testing its respiration and hydrogen transfer capacity, and by giving simultaneous inoculations in rats, he hopes to form " basic ground rules " and later to be able to make further tests of the viability of these organisms in various media. Work along these lines may later make it possible to test the viability of Myco. leprae, and the effects on them of sulphones and other drugs.

It is claimed that isoniazid-resistant tubercle bacilli may be formed with suitable dosage of this drug, and that consequently the persistence of bacilli in the sputum of tuberculous patients may not imply clinical activity of tuberculosis* or have a serious significance. In leprosy patients treated for a long time with DDS, and who still show residual bacilli, we are unable by *in vitro* culture and animal inoculation to test the viability of these bacilli, but it may be possible in future by the methods of Hanks to find out to what extent they are actually alive.

* Scadding, J. H. Lancet, July 16, 1955, p. 100.

Not only on therapeutic and metabolic lines is the relationship of leprosy to other mycobacterial diseases being studied, but also in regard to sensitization and immunity. In particular there are investigations into the effects on the lepromin test of such mycobacteria as BCG and the vole bacillus.

How are we to test for better Anti-leprosy Drugs?

If we accept the propositions: (a) that we require still better remedies for the treatment of leprosy; (b) that new drugs are being investigated for their effects on other mycobacteria, some of which are worthy of trial in leprosy, and (c) that possibly methods may in the near future become available for testing the viability of mycobacteria, how are we to set about testing new drugs for leprosy?

It would be absurd (even if it were possible or justifiable) to try to test the hundreds of possible drugs by clinical trials in leprosy patients. The first screening must be by the effects on experimental mycobacterial diseases, such as tuberculosis and rat leprosy, and clinical tuberculosis. A drug found in this way to be anti-mycobacterial and of low toxicity to animals, should be screened for its effect on human leprosy by a small pilot experiment on some six to eight patients with the lepromatous form of leprosy, who should preferably be in an advanced stage of the disease and without previous treatment. In such patients comparatively quick clinical improvement would be expected with drugs at all likely to be useful and which are worthy of further trial. Any drug not giving definite clinical signs of improvement within a few weeks in some at least of the patients should be discarded.

Any drug which gives definite signs of causing clinical improvement should be considered worthy of a wide and prolonged comparative trial, DDS being used as the control for comparison.

DDS has reached its present position as the drug of choice without any systematically planned experiment, and simply by a method of trial and error. Various widely scattered workers have reported their results, and others reading these results and repeating the trials, with or without modifications, the best methods have gradually risen to the top. There are some who uphold this somewhat blundering method, and there are others (not always the most experienced in the treatment of leprosy) who condemn it, and would have had general use suspended till a carefully planned, controlled experiment in a few special centres had sent in reports.

Whichever of these schools of thought is right, there is much more likelihood, now that we have in DDS a fairly uniformly

effective standard for comparison, that the consensus of opinion will be in favour of a carefully planned and controlled experiment.

In planning the trial the following rules are suggested:—

(a) If possible only previously untreated patients should be used.

(b) Chiefly lepromatous type patients should be used, though a few of the other types might be included.

(c) If possible there should be at least thirty on the test drug, with an equal number of controls on DDS, divided among four or five different centres. The whole planning and supervision of the trial and the final assessment of results should be carried out by one central authority. It would be well, however, for the final results to be assessed by two separate experts so as to lessen the margin of error.

(d) Centres should be chosen where there is likely to be adequate and continuous supervision for at least five years; and where the nutrition and general treatment as regards exercise, occupation and absence of other diseases are satisfactory.

(e) Patients should be chosen who are under control, and are likely to remain under treatment if necessary for at least five years, without changing their residence.

(f) Assessment of results should be based on clinical and bacteriological results, examinations being made before the beginning of treatment and then every six months. The first and last examinations (at least) should be made by the controlling expert or experts.

(g) Each patient getting the test drug should be carefully paired with one getting DDS, the two patients being comparable as regards the type, degree and duration of the disease, and as regards general health habits and other conditions.

(h) Provided there are enough patients and sufficient supervision is available at each centre, two or three drugs might be tried simultaneously in different groups, using the same DDS patients as controls for all the drugs tested at one time.

(i) If any drug proved definitely inferior to DDS after the first one or two years, then, at least in justice to the patients, it would have to be abandoned.

These rules may appear stringent and hard to carry out. If we refer to the drug trial mentioned on page 182 of this number of the Review, the results appear to be inconclusive; but the time allowed for the trial (32 to 48 weeks) appears inadequate in a slow-moving disease like leprosy, and in a prolonged trial special stress must be laid on the general conditions of the patients.

KOREA

The whole world breathed a sigh of relief when the Korean armistice was signed, but few of us have fully realised the terrible consequences of the recent war in that country. The two papers appearing in this number by Dr. Cochrane and Dr. Smith give at least a slight idea of one of the great problems with which that unfortunate country is still faced.

LEPROSY — SUMMARY OF RECENT WORK

For many years this publication has been sent twice a year to some 300 subscribers to LEPROSY REVIEW, and supplied free of charge at a considerable cost to BELRA.

A suggestion has been made that instead of doing this, a selection should be made of the abstracts which are considered most useful to our readers, and that these should be included in LEPROSY REVIEW. Before doing so, however, we are giving an opportunity to those who are at present receiving *Leprosy—Summary of Recent Work*, in case they should be able to put forward any strong objections to this suggested step.