EDITORIAL

THE ACTION OF SULPHONES ON VARIOUS INFECTIONS

Sulphones are now well established as the treatment for leprosy. In our last issue we commented on the action of sulphones on the tubercle bacillus.

There is, however, strong evidence that sulphones are active against a wider range of pathogenic micro-organisms. This is to be expected. the sulphonamides themselves show a wide but varying range of activity, and sulphones are sulphonamides. Evidence on this matter can be obtained not only by planning direct experimentation, but also by studying the infections prevalent in treated patients in leprosy institutions, and comparing the findings made with those made in other persons in the same area.

In our present issue we publish an article by Dr. Ida Mann, who studied trachoma in a leprosy institution in Australia and found the active infection completely absent while prevalent in the people of the area. She does not hesitate to attribute this finding to the action of sulphone on the trachoma virus itself, as well as on secondary infections.

Those of us who have done large scale leprosy treatment work in the pre-sulphone (and pre-antibiotic) era, and also in the post-sulphone era, cannot help being struck by the relative rarity in sulphone treated patients of the severe secondary infections of hands or feet, with ascending cellulitis and gangrene, which used to be so troublesome. Infections with gram-positive organisms are now very rare; staphylococcal infections, however, remain fairly common.

The rarity of pneumococcal infection and also of meningococcal infections in sulphone treated patients in areas where these infections are prevalent, has been noted. It is found, by direct and indirect observations, that sulphone has little influence on gonococcal infections.

One infection in which sulphones have been found active is toxoplasmosis. This is a protozoal infection, discovered in 1909 in animals, and since 1939 found to be the cause of disease in human beings. The toxoplasmic etiology of certain types of congenital encephalomyelitis and ocular damage, of certain types of acute encephalitis in older children, of a spotted fever-like disease and pneumonitis in adults, now rests on the firm foundation of demonstration of the organisms in the tissues, recovery of the organisms by passage in experimental animals, and demonstration

of cross-immunity with toxoplasma of animal origin. It is also found that other diseases of obscure aetiology may be caused by toxoplasma, and tests to reveal antibody may in certain countries give positive results in 50 per cent or more of the population over 20 years of age. In England figures of 5.2 %[1] and 7%[2] have been cited, even in children. Now this protozoal infection responds to treatment with sulphonamides, especially to sulphadiazine, sulphamethazine and sulphamerazine, but also to sulphones, (and, it appears, to daraprim). The action of sulphonamides against other protozoal infections is usually very slight.

There have been reports that sulphones are active against filarial and fungal infections, but these have not been confirmed.

There are however these definite indications, here quoted, that sulphones are active against at least one virus (that of trachoma) against certain cocci, bacilli, and mycobacteria, and against at least one protozoon.

In only one of these infections, leprosy, does sulphone at present appear to be the best available agent; in the other infections mentioned, other drugs appear preferable.

1 Macdonald, A. (1950), "Lancet," ii, 560.
2 Cathie, I. A. B., and Dudgeon, J. A. (1953), "Great Ormond Street Journal," 5, 13.

THE LEPROSY BACILLUS AND THE HOST REACTION TO IT

The present issue contains a paper discussing this subject; this paper was contributed to a recent symposium on the tubercle bacillus (with the leprosy bacillus as an added item) organised by the Ciba Foundation in London. This paper brings together material from widely scattered sources in a manner which may not be without interest; we have not seen any other paper which attempts to cover the same ground. In this paper occur the following passages:—

> "I would here mention and emphasize one most striking feature of leprosy, the complete cellular inactivity to the enormous numbers of leprosy bacilli seen in the typical lepromatous case; this I believe has no real parallel in tuberculosis unless it be in the tuberculin negativity of acute miliary tuberculosis, or of advanced generalised tuberculosis . . . .
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> "One could surmise that with the marked infiltration of the reticulo-endothelial system which is characteristic of lepromatous leprosy, the normal production of protective antibodies by this system might be upset; such findings have been recorded in other affections of this system, for example in Hodgkins disease and in sarcoidosis, in which tuberculin

sensitivity may be suppressed (Hoyle, Dawson and Mather, 1954). But in lepromatous leprosy, there is little or no suppression of tuberculin sensitivity or of other forms of sensitivity or immunity, although lepromin sensitivity is completely absent. No, the anergy, insensitivity, lack of effective response, or whatever name one likes to give to this strange phenomenon, is specific for the leprous bacillus and its antigens. It might be that in lepromatous leprosy, the protective antibodies to the bacillus are produced, but that they are blocked or inactivated in some way, probably by some mechanism associated with the infection. An attempt to study this idea seems worthwhile.''

Also in the present number is reviewed an article by Ridley, part of which bears on this same problem. He quotes an old (1908) report that the serum of a patient desensitised by repeated injections of tuberculin, when mixed and incubated with tuberculin, was capable of inactivating this tuberculin, as shown by the negative results produced by the mixture in the Mantoux test in tuberculin positive persons. Ridley rightly thought the idea worth study in leprosy. He got two lepromin-positive patients and gave each one tests with four intradermal injections (a) ordinary lepromin; (b) lepromin—normal-serum mixture incubated for 24 hours; (c) and (d) lepromin—lepromatous-serum mixture incubated for 24 hours. Injections (a) and (b) gave positive results in both patients. In one patient, injections (c) and (d) gave positive results but weaker than with (a) and (b); in the other patient injections (c) and (d) gave negative results. Ridley interprets these findings as suggesting the suppression of lepromin sensitivity by circulating antibody present in lepromatous serum.

It is a pity that only two patients were available for testing and, further, that only the early 24-48 hrs. reaction was recorded, for the late reaction is usually considered more constant and more significant. In fact, the view that the early 24-48 hrs. reaction and the late 2-5 weeks reaction to lepromin are of the same significance may be untenable, particularly if the finding of Fernandez is confirmed, that by desensitising with leprosy bacillus protein, one can abolish the early reaction, yet maintain the late reaction.

Dr. Ridley in a personal communication says that a third person has been tested, with apparently similar results, and, moreover, that the inactivation by lepromatous serum is dependent on the presence in the serum of complement, and can be inhibited by previous maintenance of the serum to half an hour at 57°C to destroy complement.

This whole subject is one that is full of interest and calls for

investigation. Moreover, investigation of this matter calls for no highly specialised technique or equipment. Work along these lines is already being undertaken by certain workers, and more light on this subject should soon be available. If it is confirmed that lepromatous serum does contain a substance which can inactivate lepromin, and that normal serum does not, this finding will throw new light on the nature of lepromatous leprosy.

The Editor however feels that his own studies, as well as the work of others, as summarised in the article in the present issue, tends to indicate that the presence of reaction to lepromin, and particularly the late reaction to lepromin, is quite independent of the presence of circulating antibodies, and that immunity to leprosy is almost entirely cellular and not humoral. Ridley himself, although he suggests a humoral defence mechanism in leprosy, writes " There are two theoretical reasons why the lepromin reaction in leprosy might be negative (i) that there is no hypersensitivity because there is no fixed antibody, and (2) that the presence of fixed antibody is masked by circulating antibody which neutralizes antigen before it reacts in the tissues." Most students of leprosy have considered that the absence of fixed antibody was the probable explanation. Ridley's findings justify a further consideration of the second hypothesis.

One point in Ridley's paper calls for comment. In cases of leprosy he found no antibody to tuberculin, as revealed by complement fixation tests. He makes no reference to the large mass of previous work on this subject which shows that with antigen prepared from the tubercle bacillus, and also other acid-fast bacilli, complement fixation tests in lepromatous leprosy are nearly always positive. This matter was reviewed by Cooke (1919) and Lowe and Greval (1939). More references to this subject appear in Lowe's article in the present issue. In this matter Ridley's findings appear to be at variance with those of all other workers. If Ridley had prepared his antigen from the tubercle bacillus itself and not from tuberculin, his results would almost certainly have been different.

THE PROGRESS OF ANTI-LEPROSY WORK IN AFRICA

In recent numbers of this journal there has been some discussion on this subject, and some differences, not of opinion, but of emphasis, have become apparent in our Correspondence section. Some editorial comment may clear up misunderstandings and make further correspondence unnecessary.

Twenty years ago anti-leprosy work in most parts of Africa was very limited in quantity and often poor in quality; this was true of Africa as a whole, including British administered areas. The last twenty years have seen the establishment and development in certain parts of Africa of anti-leprosy work on a surprisingly large scale, and this has resulted in a complete change in the outlook. To this change numerous organisations, government, local administration, missions, BELRA, Toc H etc. and many individuals have made important contributions.

Anti-leprosy work in the British Commonwealth and elsewhere owes much to the persistent effort and advocacy of Sir Leonard Rogers over many years; at the age of 86 he contributed to our January, 1954 number an article on " Leprosy Incidence and Control in East Africa, 1924-1952 ". This article provoked certain criticisms from Dr. J. A. K. Brown.

Now Dr. J. A. K. Brown is a worker to whom anti-leprosy work in Africa owes much. It was his pioneer work with the Methodist Mission in East Nigeria in the early 1930's which was the turning point in anti-leprosy work in that country, and which contributed greatly to the subsequent developments there and elsewhere. Unfortunately his work there ended in 1936, when he returned to England. In recent years he has returned once more to leprosy work in Africa, where he is in charge as a Government officer of anti-leprosy work in Uganda, where important progress is recorded. Dr. Brown's letter pointing out certain inaccuracies in Sir Leonard Rogers' article was published in the July, 1954 number, and also Sir Leonard Rogers' comments on these criticisms. As both Dr. Brown in his letter, and Sir Leonard in his reply, point out, it is the " composite co-operative effort " of organisations and individuals that has made the work possible. The organisations included government, missions, and local administrations, and BELRA with Sir Leonard Rogers as Medical Adviser, and Dr. E. Muir as Medical Secretary from 1935. Prominent among the individuals in the 1930's were Dr. J. A. K. Brown and his successor Dr. T. F. Davey.

In the 1930's, BELRA's contribution to leprosy work in Africa in personnel and funds was, to begin with, relatively small, but grew steadily. Sir Leonard Rogers has recently written to the Editor stating that the Annual Medical Report of Uganda for 1931 shows a figure of £9,000 (not £15,350 as he previously stated) as paid by BELRA. In recent years Africa has been BELRA's main field of work, and contributions in workers and money have been on a large scale—over £200,000 in the last five years. But still BELRA and its workers are only members of a group of organisa-

tions and individuals contributing staff, funds, ideas, and willing service to this " composite co-operative effort ", without which no anti-leprosy work can progress.

LEPROSY TREATMENT IN EAST NIGERIA

A recent letter from Dr. T. F. Davey, now (among other duties) continuing research work at the Leprosy Settlement, Uzuakoli, Nigeria, contains the following passages which may be of general interest.

" THIOSEMICARBAZONE.

I have been through the T.B.1 patients for my own sake and think the effort was worth while. The July *Leprosy in India* has arrived with your letter in it.* The main points of my study appear to be as follows:—

(a) Degeneration in lepromatous patients is to be expected in a considerable proportion by the third year (30% of your cases), but with one exception all those concerned have done extremely well subsequently on D.D.S. There is thus no evidence of cross resistance.

(b) In view of this your suggestion of alternating treatment needs going into carefully. One thing that impresses me from the T.B.1 records is the apparent speedy reduction in numbers of bacilli in smears during the first few months. This later tails off of course, but is nevertheless noticeable, and it may therefore be good to start with T.B.1 for a year and then change to D.D.S. Here your considerable number of patients who have had one year on T.B.1 will provide information fairly soon, as already many of them have now had nearly a year's treatment on D.D.S. as well.

(c) So far there have been four relapses among tuberculoid patients discharged after T.B.1 treatment. That is 10% of such discharges. One relapse among lepromatous patients discharged. In all cases the period of treatment would, I am sure, be considered quite adequate."

(A later letter states: " I have to report another relapse, this time in a patient who had a full three years course of T.B.1 before discharge. He relapsed 11 months later, with strongly positive bacteriological findings in multiple smears, bacilli having a normal appearance.')

* The findings recorded in that letter have since been given in detail in " Leprosy Review,' Oct. 1954, p.186, and in the " Lancet," Nov. 20, 1954, p.1065.

" DAPSONE.

I can find no evidence here or at other Nigerian Settlements of resistance developing to D.D.S. We are carefully recording the appearance of the bacilli in all smears done. Some of the old chronic patients still continue to have positive smears, but almost without exception they do not seem to demonstrate the continuance of active looking bacilli, but rather the slow elimination of acid fast debris.'

" OTHER TREATMENTS.

You may be interested in some lesser matters. We are putting as many ulcer patients as possible into walking plasters, with very encouraging results. There are now 20 empty beds in the hospital for one thing, and a much better opportunity to deal with general surgical conditions in clinic patients. A number of exceedingly chronic ulcers have healed completely.

Also we are operating on nerves as soon as any acute signs of neuritis appear, keeping careful records so that ultimately the late results of operative treatment can be assessed. It is here that Dr. Fisher's experience in plastic surgery comes in useful, as she uses special little needles and other means of reducing trauma to a minimum."