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EDITORIALS

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MODERN TREATMENT OF LEPROSY [a]

The leprosy hospital or settlement used to be a kind of medical slum. Though the unfortunate patients evoked pity, their case was so hopeless that little could be done except nurse them until they died, and even that took painfully long. But the last 20 years have seen great advances. Leprosy has changed from being a hopeless horror to being a relationship between host and invading pathogen that can be successfully challenged, and there is the cheerful conviction that most patients with leprosy can eventually be cured, though it may still take a long time. The fundamental advance during this period has been the introduction of dapsone (diaminodiphenyl sulfone) by J. Lowe[1] and others. This has now become the standard treatment, given in doses approximating to 300 mg. twice weekly. It has the advantages that it cures most patients in the long run, it never produces resistant bacilli, it seldom produces dangerous complications if given with reasonable care, and it is cheap. Since great numbers of patients must be treated for long periods in poverty-stricken countries, this last attribute is important. All the same, dapsone is not the perfect drug for leprosy, and there have been many attempts to produce drugs which act more rapidly or which are less apt to produce untoward effects or lepra reactions.

In the first place there have been attempts to modify or mask the sulphone molecule by substituting one or both of the terminal amino groups, or by using diaminodiphenyl sulphoxide (which has one less

[a] This note appeared as an editorial in the *British Medical Journal* **2** (1960) 655-657, and is reprinted with permission.

[1] LOWE, J. Treatment of leprosy with diamino-diphenyl sulphone by mouth. Lancet **1** (1950) 145-150.

oxygen atom than dapsone).[2] Some of these compounds may have slight advantages over dapsone, but they are not so great as to supplant the parent compound. A more hopeful compound is Ciba 1906 (D.P.T., 4-butoxy-4-dimethyl-amino -diphenol-thiourea). This was first tried by T. F. Davey and G. Currie five years ago and considerable experience has now been gained with it.[3] Briefly, it is given orally as 2 g. daily for an adult. It is slightly more active than dapsone, as judged by the disappearance of bacilli in lepromatous cases. In two to three years signs of drug resistance may appear, so it should not be continued after that period. Its chief advantage is that it is less toxic than dapsone; in particular, it is less harmful to the liver and it has less tendency to provoke lepra reactions or erythema nodosum. Accordingly it is the drug of choice for debilitated patients or for those on dapsone who have complications such as psychosis, neuritis, or the reactions already mentioned. It is rather expensive, especially when the much bigger dosage is taken into account; on the other hand, if it allows treatment as an out-patient instead of an in-patient it may be an economy in the long run.[4] There is some evidence that its therapeutic effect depends on its conversion to a more active metabolite.

The next drug was "Etisul" (diethyldithiol *iso*phthalate), which is somewhat unconventional. Compounds of this type (ethylmercaptans) had long been known to be active against acid-fast bacilli, but their clinical application was hindered by their stench. However, acceptable preparations have been provided by the addition of suitable perfumes, and Etisul can now be given twice weekly by inunction over a large area of the body. When given to lepromatous patients in this way Davey[3] found that there was often a remarkable reduction in the number of bacilli in biopsy specimens of skin, a change in their morphology, and a distinct clinical improvement in the patient. These effects are greater than can be produced by other drugs and they have been confirmed elsewhere. After three to six months signs of drug resistance may appear, and the patients tend to become weary of the treatment. Accordingly this compound is best given in conjunction with dapsone or Ciba 1906, and after three months the Etisul is discontinued.

Many other drugs have been tried,[2] but none have been outstandingly successful. Cortisone and related steroids have been found valuable in controlling lepra reactions provoked by dapsone; and unless their administration is unduly prolonged they do not seem to do harm by weakening the body's defences against this infection.

Changes in the morphology of bacilli during treatment with Etisul

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[2] Bushby, S. R. M. The chemotherapy of leprosy. Pharmacol. Rev. **10** (1958) 1-42.

[3] Davey, T. F. Some recent chemotherapeutic work in leprosy: with a discussion of some of the problems involved in clinical trials. Trans. Roy. Soc. Trop. Med. & Hyg. **54** (1960) 199-206; discussion pp. 207-211.

[4] Garrod, J. M. B. Two years' experience with diphenylthiourea (DPT or Ciba 1906) in the treatment of leprosy. Leprosy Rev. **30** (1959) 210-214.

or even with dapsone can be seen in the ordinary Ziehl-Neelsen smear, but they are better studied by the electron microscope.[5,6] When the disease is active and progressing, many of the bacilli are normal in shape and presumably alive, but even at this stage many appear degenerate and are presumably dead. When disease is regressing, either spontaneously or under treatment, most of the bacilli are certainly defunct. They are corpses of bacilli which the body finds difficult to digest and remove. In Ziehl-Neelsen smears they appear granular and stain poorly; they can be ignored as evidence of active disease. Reactivation of the disease (if it should take place) is preceded by the reappearance of bacilli with normal shape and staining reactions.

Among the other aspects of leprosy on which research is proceeding, the nature of the lepromin reaction has been critically reconsidered. It had always been assumed that a positive lepromin reaction was analogous to a positive tuberculin reaction, and that it indicated hypersensitivity of the body induced by the infection specifically to certain chemical fractions of the leprosy bacillus. But now evidence is accumulating [7] that the lepromin reaction may depend only on raised sensitivity to almost any foreign substance introduced into the skin. Secondly, great efforts are being made to induce leprosy bacilli to multiply either in laboratory animals or in tissue cultures. Limited multiplication—namely, two to four generations—of the rat leprosy bacillus has been obtained in tissue cultures by J. H. Wallace and colleagues [8] and R. J. W. Rees and P. C. Wong.[9] Material from lepromatous patients has also been inoculated into animals and growth of acid-fast bacilli has been obtained in black mice,[10] in hamsters,[11] and in chimpanzees.[12] The past history of leprosy is strew with so many premature claims that all reports must be regarded with scepticism until it is proved beyond all doubt whether the bacillus which has been isolated is really Hansen's bacillus or only some previously unrecognized mycobacterium, of which unfortunately there are many. Nevertheless, leprosy has now changed from a subject of despair to one of active, and optimistic, research.

This broad survey, which goes considerably beyond treatment, will not meet with full approval or acceptance in all respects and in all sectors. There are, for example, leprologists who would have given priority to thiacetazone (TB-1) as the drug of second choice, alternative to DDS. Then there are those who would have qualified the

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[5] McFadzean, J. A. and Valentine, R. C. The examination and the determination of the viability of *Mycobacterium leprae* by electron microscopy. Leprosy Rev. **31** (1960) 6-11.

[6] Rees, R. J. W., Valentine, R. C. and Wong, P. C. Application of quantitative electron microscopy to the study of *Mycobacterium lepraemurium* and *M. leprae*. J. Gen. Microbiol. **22** (1960) 443-457.

[7] Kooij, R. and Gérritsen, Th. Positive "lepromin" reactions with suspensions of normal tissue particles. Internat. J. Leprosy **24** (1956) 171-181.

[8] Wallace, J. H., Elek, S. D. and Hanks, J. H. Limited multiplication of *Mycobacterium lepraemurium* in cell cultures. Proc. Soc. Exper. Biol. & Med. **97** (158) 101-104.

[9] Rees, R. J. W. and Wong, P. C. Limited multiplication of *M. lepraemurium* in tissue culture. Nature **181** (1958) 359-360 (correspondence).

[10] Chatterjee, K. R. Experimental transmission of human leprosy infection to a selected, laboratory-bred hybrid black mouse. Internat. J. Leprosy **26** (1958) 195-204.

[11] Binford, C. H. Histiocytic granulomatous mycobacterial lesions produced in the golden hamster (*Cricetus auratus*) inoculated with human leprosy. Negative results in ten experiments using other animals. Internat. J. Leprosy **26** (1958) 318-324.

[12] Gunders, A. E. Progressive experimental infection with *Mycobacterium leprae* in a chimpanzee; a preliminary report. J. Trop. Med. & Hyg. **61** (1958) 228-230.

story of Etisul as applicable to African patients, but not to those in, for example, India.

Changes of morphology of the bacilli in the course of treatment, in the way of granulation and lessened intensity of staining, was observed back in the chaulmoogra days, long before "even dapsone" came into the picture—but not limited to "biopsy specimens" of the skin. The present emphasis doubtless results from recent studies with the electron microscope. It may be a good thing that the matter should be emphasized and investigated further, by more ordinary and practicable means; perhaps some day cases will cease to be categorized as "active" on the basis of the presence of "corpses" of bacilli.

There are those who would seriously question the statement that it has always been assumed that the reaction to lepromin is analogous to the one due to tuberculin hypersensitivity. That can be true only of the early reaction, and not of the late reaction, which is the one which counts in practice. The statement that the reaction may be induced by almost any foreign substance introduced into the skin is also open to question. It is correctly said that the matter is one still subject to research.

This editorial has been criticized on other grounds by R. G. Cochrane, in a letter which, slightly condensed, is also reproduced by permission from the *British Medical Journal* (**2**(1960) 1671).

SIR: As one who has been doing leprosy work for 36 years, I was naturally interested in your leading article on the modern treatment of leprosy. . . I regret, however, that it distorts the picture quite considerably. It is not only unfair, but unjust, to indicate that the leprosy hospital or settlement of 20 years ago "used to be a kind of medical slum." It is perfectly true that in 1924, when I first went out to India, medical conditions in many leprosy hospitals left much to be desired, but conditions improved rapidly in the subsequent decade. . .

One statement which must be refuted is that "it [i.e., dapsone] has the advantage that it cures most patients in the long run; it never produces resistant bacilli." If dapsone cures the majority of patients, what happens to those patients who are not cured? It would be a very extraordinary drug if resistance never developed under therapy no matter how long the drug is used. There is no question that modern treatment of leprosy has revolutionized the whole outlook of the disease and has made possible the great advances in orthopaedic surgery and plastic surgery. Nevertheless, it does a disservice to the cause of leprosy for the general impression to go abroad that we now have the disease conquered as far as therapy is concerned.

[The writer then mentions the "6 to 16%" of all lepromatous cases which are persistently positive; those that have been under treatment for 12 to 15 years but remain bacteriologically positive; and those that relapse.] Furthermore, if resistance never forms under dapsone therapy, what is the reason for the constant search for new remedies? Every new remedy is hailed with a flare of trumpets and as a cure for leprosy, until those who are a little more cautious begin to find the disadvantages of the remedy.

In the old days under chaulmoogra therapy, when we used to cure, sceptics stated that the disease would have naturally subsided without any therapy at all. To-day we seem to discount any question of the natural subsidence of the disease, and yet there is sufficient evidence to show that over 75% of all lesions of leprosy in childhood do not advance to the more active stages, and, further, that between 50 and 75% of these lesions

heal spontaneously. Furthermore, in the old days we never bothered to treat certain tuberculoid cases, for we knew that tissue response was so effective that the disease would become naturally arrested. To-day, credit is always given to dapsone, whether that credit is justified or not.

[This letter ends with an appeal that leprosy be regarded with a less optimistic outlook but as one of the most profitable diseases for study—as much medicine as tuberculosis and other diseases, and one in which increasing numbers of medical men should specialize.]

A dissenting response with respect to certain features of the foregoing letter appeared in one by Spencer Reed, from Bali, Indonesia (*British Medical Journal* **2** (1960) 1672).

SIR: Though a full-time worker in leprosy for only four years, I must nevertheless take up cudgels with my former mentor Dr. Robert Cochrane . . . for accusing your leader writer . . . of "distorting the picture quite considerably." I just cannot understand why Dr. Cochrane prognosticates so gloomily about dapsone and the other new drugs when there is now ample clinical evidence throughout the world of their efficacy. However, in this letter I shall refer to results in Bali alone.

He states that 50-75% heal spontaneously. Of course we all know that, as tuberculoid cases normally have a high immunity. But what of the lepromatous ones with low or no immunity, and tuberculoid ones that go into reaction, resulting, without treatment, in permanent damage to the nerves? Formerly all these were doomed to progressively advancing mutilations which, when sufficiently repugnant, caused them to be thrown out of their villages as outcasts. . . Now dapsone has completely changed the picture, and every new patient can be assured such a fate will never be his.

Here in Bali the contrast between the pre- and post-dapsone patients is most striking. All the former—300 of them—who were not lucky enough . . . to heal spontaneously have now been gathered up to live in six leprosaria by the sea, clothed and fed by the government. Practically all of them have revolting and pathethic mutilations. In marked comparison are the 2,000 out-patients who are making dramatic progress under dapsone. This they receive regularly at a set time and place every two weeks at one of 90 different places throughout the island. . . Not only is ugly infiltration receding, but to all intents and purposes the development of contractures and mutilations is now a thing of the past. Moreover, and this is of vital importance, almost 100% are still fully accepted members of the community: not one has been hounded out of his normal occupation. Within the last two years, patients have been allowed to join in the communal rice gathering, for example, and carpenters are flooded with orders for work. A further objective proof of the efficacy of dapsone is that also within the same period 500 of our present patients have presented themselves *voluntarily* for treatment, and the great majority of these are in the earliest stages without deformities having already developed, and this because Bali has seen with its own eyes during the previous two years the results of dapsone. No wonder we here, together with your leader writer, can look forward to the future with cheerful confidence.

[Induction of treatment, with good results and negligible toxic effects, is with only 50 mg. a week.] And that small dose can be given to a semi-advanced lepromatous case for a year with the most wonderful results. Certainly 10% may remain bacillary positive for many years. But what is that to a patient who no longer is an object of loathing? . . . Certainly a proportion will develop reactions. But all these can quickly be brought into a central ward, where rest to swollen nerves and other treatment . . . will in almost all cases lift the patients over this hurdle. One can now say that no reaction case properly treated should develop permanently damaged nerves.

Dr. Cochrane does indeed admit that "modern treatment has revolutionized the whole outlook of the disease," but paradoxically continues that this "has made possible

the great advances in orthopaedic surgery and plastic surgery," but I would like to make the point that it is the *neglect* of the use of modern drugs that alone had made this advance possible, giving the surgeons much fodder.

[In response to the request of WHO for data on mutilations, in connection with a world-wide rehabilitation scheme] I am now . . . re-examining all our out-patients, and it is already certain that my statistics will show that, in a field campaign where practically 100% of patients are getting treatment regularly, there is no need for such a costly scheme as there would be so few to rehabilitate.

This optimistic picture brought a comment from Dr. H. W. Wheate, of Tanganyika (*British Medical Journal* **1** (1961) 75).

SIR: Dr. Spencer Reed's letter on the treatment of leprosy was of great interest. He rightly emphasizes that sulphone treatment not only prevents the advance of the disease to mutilation but also prevents the social and economic complications of the disease. One cannot, however, ignore two facts: in some cases sulphone therapy precipitates reactions which lead to permanent nerve damage; and the very long period of treatment required presents serious social and administrative problems.

Dr. Reed has confined his remarks to Bali, and he would, I am sure, agree that they do not apply universally. In Tanganyika, for example—a vast country with 100,000 cases of leprosy—we cannot be so sanguine about reactions and cannot possibly agree with Dr. Reed that "*all* these can *quickly* be brought into a central ward" (my italics). On the other hand, there are parts of the country where the local problem is on a similar scale to that in Bali and has been tackled by a similar concentrated effort. Here, we can say with Dr. Reed, "(They have) seen with (their) own eyes the results of dapsone." But it must be emphasized that one just cannot achieve results like this *en masse* with only an effective drug. Staff, money, and a good organization are even more important.

It may be true, in Bali, that "no reaction case properly treated should develop permanently damaged nerves," but if we in Tanganyika wait until the reaction has occurred we are often too late. Further, our experience is that "properly treated" usually means "treated with a drug other than dapsone"—and even then we are not always successful.

Finally, I think we must avoid undue optimism about the long-term effects of sulphone therapy. I am seeing lepromatous cases who have been under apparently effective sulphone therapy for five, six, or seven years suddenly develop acute neuritis. "Properly treated," permanent nerve damage can be avoided, but they tend to relapse and one can never be quite sure that they will not end up with some degree of deformity.