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## EDITORIALS

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### SULPHONE TREATMENT OF LEPROSY

It is now more than five years since a derivative of diamino-diphenyl sulphone was found to be effective in the treatment of leprosy. The Pan-American Conference, held in Rio de Janeiro in 1946, gave unqualified support to the sulphones. At the International Congress held in Havana in 1948, despite the more cautious report of the committee on therapy, the general vote indicated that a great majority accepted these new drugs as of choice in lepromatous leprosy.

The sulphones have therefore become established as a significant advance in therapy, and it may be well to take stock of the position in the endeavor to maintain a proper and helpful perspective. Before discussing their action and indicating why a cautious attitude toward them must still be maintained by the leprologist, one should draw attention to certain fundamental principles of successful leprosy therapy applied on a mass scale. If the large number of cases in the world are to be benefited by any therapy, three conditions must be fulfilled: (1) the drug must be cheap; (2) it must be easy of administration; and (3) it must be of sufficiently low toxicity to permit its use by relatively untrained personnel.

Because the high dosages of sulphones that it is customary to use result in high costs, efforts were directed in the writer's

work<sup>1</sup> to discovering a preparation and method of administration which would be effective and safe and at the same time less expensive. Of the sulphones given by mouth, considerable proportions are wasted because of nonabsorption. Of promin administered intravenously, much of the daily large dose is very quickly eliminated in the urine; and, furthermore, this method is expensive as regards the labor of trained personnel which is involved. Attention was therefore directed toward the injection of other forms of sulphones by other routes.

As a result of our investigation, two preparations have been shown to be effective in lepromatous leprosy when injected subcutaneously, namely: (1) a 50 per cent aqueous solution of sulphetrone in a dosage of 5 cc. twice a week; and (2) a 25 per cent suspension of diaminodiphenyl sulphone (DDS)<sup>2</sup> in arachis (groundnut, or peanut) oil in a dosage of 5 cc. twice a week. The former remedy appears to be nontoxic, while the latter has given rise to toxic symptoms sometimes of alarming proportions. More recent work, however, indicates that probably the commencing dose of 2.5 grams per week was too high, and that satisfactory results can be achieved without toxic effects by as small a dose as 1.0 to 1.5 grams per week. With regard to the cost of the drug used in treatment, it is an important fact that 5 grams of sulphetrone per week by injection has been shown to be probably as effective as 5 grams per day by mouth. This, therefore, demonstrates that treatment with the sulphone derivatives by injection is by far the more economical method.

Lowe,<sup>3</sup> in West Africa, has found that when given by mouth the parent substance, DDS, unlike some of its derivatives when

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<sup>1</sup> COCHRANE, R. G. A comparison of sulphone and hydnocarpus therapy of leprosy. *THE JOURNAL* **16** (1948) 139-144; also Mem. V Congr. Internac. Lepra, 1948; Havana, 1949, pp. 220-224. COCHRANE, R. G. New developments in the therapy of leprosy. Proc. Fourth Internat. Cong. Trop. Med. & Malaria, Department of State, Washington, vol. 1, pp. 374-381; *THE JOURNAL* **17** (1949) (p. 283). COCHRANE, R. G., RAMANUJAM, K., PAUL H. & RUSSELL, D. Two-and-a-half years' experimental work on the sulphone group of drugs. *Lep. Rev.* **20** (1949) 4-64 [see abstract in this issue, p. 354.]

<sup>2</sup> To minimize confusion it has been necessary to adopt a single form of abbreviation for 4,4'-diaminodiphenyl sulphone. The writer of the present note uses "D. A. D. P. S." and has cited Lowe as using "DADS." On the other hand workers in the United States, including some of the first to employ the substance in experimental tuberculosis, refer to it as "DDS;" and *THE JOURNAL* will employ that form.—EDITOR.

<sup>3</sup> LOWE, J. Annual Report, 1948, of the BELRA Research Unit of Nigeria, unpublished; also personal communication. [See this issue, p. 197.]

given by that route, is almost completely absorbed by the alimentary tract, and that a dose of 0.3 gram per day will maintain consistent and adequate blood levels. He commences with 0.1 gram per day and reaches the full dose in a fortnight or three weeks. Even though this dosage, given orally, is relatively safe, the greatest precautions would have to be taken against misuse lest patients or their attendants, in their enthusiasm, get access to the remedy and take a greater number of tablets than prescribed.

Another question which is relevant in a discussion on the sulphones is that of their mode of action. In the first place it is believed by many that, whatever the derivatives used, its relative effectiveness depends on the ability of the body to break it down to the original diaminodiphenyl sulphone. Feldman<sup>4</sup> held that view for promin and diasone when given by mouth, and M. I. Smith and associates<sup>5</sup> have recently asserted that "certain disubstituted derivatives like promin, diasone and possibly sulphetrone" are metabolized to DDS. On the other hand, Brownlee and associates<sup>6</sup> say that sulphetrone is apparently not degraded to that substance, and Sharp and Payne<sup>7</sup> assert that promacetin is unchanged in the body. However Lowe and his coworkers<sup>8</sup> believe that all of the sulphones act by virtue of their degradation to the parent substance, and they have brought forward some evidence to support this contention.

At the present moment the smallest effective dose of DDS, as compared with sulphetrone, is 2 grams per week of the former against 5 grams per week of the latter. It may be found, as already stated, that the effective dose of DDS is considerably smaller—possibly as low as 0.5 gram per week. If so, it would indicate that the sulphone derivatives do act in proportion as they can be degraded to the parent substance; and, if that is correct, then one must agree with those who believe that further search for more effective and less toxic sulphone preparations is

<sup>4</sup> FELDMAN, W. H. "The Chemotherapy of Tuberculosis"—Including the Use of Streptomycin. The Harben Lectures, 1946. J. Roy. Inst. Publ. Health & Hyg. **9** (1946) 267-288, 297-324; 343-363; reprint, page 44.

<sup>5</sup> SMITH, M. I., JACKSON, E. L., CHANG, Y. T. & LONGENECKER, W. H. Metabolic fate of 4,4'-diaminodiphenylsulfone (DDS) in the rabbit and its isolation from urine. Proc. Soc. Exper. Biol. & Med. **71** (1949) 23-25.

<sup>6</sup> BROWNLEE, G., GREEN, A. F. & WOODBINE, M. Sulphetrone: a chemotherapeutic agent for tuberculosis; pharmacology and chemotherapy. British J. Pharm. & Chemoth. **3** (1948) 15-28.

<sup>7</sup> SHARP, E. A. & PAYNE, E. H. The present status of the sulfones in therapy. THE JOURNAL **16** (1948) 157-172.

unlikely to be successful. Future work, therefore, should be concentrated on determining the lowest effective dose of the sulphone preparations, particularly of diaminodiphenyl sulphone, and on the extension of studies of the absorption and excretion of these drugs. In particular, further evidence should be sought with reference to the complete or partial degradation of the sulphone derivatives to the parent substance.

Whenever a chemotherapeutic agent or an antibiotic has shown itself effective *in vitro* against acid-fast bacilli, or valuable in the treatment of tuberculosis, a clinical trial should be undertaken in leprosy. Our minds should always remain open, for it would be detrimental to progress if too optimistic a view of the effectiveness of the sulphones were held, and if in consequence workers should become satisfied with the results now being obtained because of the marked superiority of these preparations over the hydnocarpus (chaulmoogra) group of drugs in advanced lepromatous leprosy.

It is known that all sulphone remedies, after a few months, cause the microorganism of leprosy to become beaded and granular, bipolar forms becoming more numerous. This process continues until the bacilli are reduced to acid-fast dust. It is tempting to speculate that these are degenerate forms, but there is as yet no evidence for this idea although it appears logical to assume that these forms appear whenever the environment is unfavourable for the multiplication of *M. leprae*.

It has been suggested that the sulphones act by eliminating bacillary infection from the blood vessels and the blood stream, but apart from the work of Fite and Gemar<sup>8</sup> this idea has not been followed up. In so far as the sulphones, particularly in the case of DDS, are retained in the tissues for a long time after their administration has stopped, it probably is correct to assume that these drugs have a chemotherapeutic effect on the bacilli wherever their concentration is adequate. We believe that sulphones act directly on the bacillus; that is, that they are chemotherapeutic agents. There are, however, certain anomalous findings to which attention must be drawn, for in taking note of them the danger of excessive optimism will be checked.

The first of these anomalies is that, in a large proportion of cases, all sulphones appear to cause the disease temporarily to increase. This will be seen if the following criteria are taken as

<sup>8</sup> FITE, G. L. & GEMAR, F. Regressive changes in leprosy under prominin therapy. Southern Med. J. 39 (1946) 277-282; reprinted in THE JOURNAL 15 (1947) 431-439.

signs of deterioration: (1) lepra reaction; (2) exacerbation of clinical signs without pyrexia; (3) deterioration of the bacteriological index. Judged by these standards it will be found that a considerable number of cases, possible over 50 per cent, show deterioration before improvement sets in. The phenomenon of erythema nodosum leprosum described by Wolcott<sup>9</sup> is not uncommon, especially with injections of DDS. It may be that reactions are most frequent when the higher dosages are used. Whether or not they are ultimately beneficial, the patient's progress towards recovery being hastened, is a question which as yet has not been answered. Reactions appear to be least frequent and least severe when an aqueous solution of sulphetrone is used. This in itself suggests that a preparation which does not produce reservoirs of the drug in the tissues is less likely to show untoward reactions than when such storage occurs.

The second anomalous phenomenon is the erratic nature of the action of the sulphones. For instance, one patient may become bacteriologically negative within 20 months, whereas others may show comparatively little bacteriological improvement after even longer periods of treatment. There may again be some relationship in the fact that some patients tolerate larger doses than others, and therefore the total quantity of sulphones given over a similar period is greater; and the rest periods may be fewer. On the other hand one is tempted to speculate that the bacillus is more sensitive to the sulphone group of drugs at a certain stage in its cycle than at others. The explanation does not lie in the fact that some cases come earlier for treatment than others, for improvement in sulphone therapy does not seem to bear direct relationship to that factor.

It is generally accepted that sulphones are particularly useful in lepromatous cases, especially those which do not respond to adequately administered hydnocarpus oil. Therefore, until an inexpensive and safe method of administration is established, these drugs should still be used only in those lepromatous cases which do not respond to hydnocarpus therapy—unless of course the hydnocarpus derivatives are difficult to procure because of modern complexities in export. If, as it is hoped will occur, the sulphone preparations become so reduced in price as to be available for all, then all active lepromatous cases should be so treated. Up to now there has been no concrete evidence that sulphones act

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<sup>9</sup> WOLCOTT, R. R. Erythema nodosum in leprosy. *THE JOURNAL* 15 (1947) 380-388.

better if administered concurrently with hydnocarpus oil or its derivatives.

The question of treating active neural cases—tuberculoid or simple maculoneural—with the sulphones is still *sub judice*. At Havana, de Souza Lima<sup>10</sup> reported that both chronic reactional and torpid tuberculoid cases, in both the leprosarium and the dispensary, did well under such treatment, and he intimated that favorable results were obtained in simple macular (“in-characteristic”) cases. Lowe has recently given fresh support to this view. The results of de Souza Lima are of extreme interest because he recognized the well-known tendency for tuberculoid cases to undergo spontaneous recession. I am strongly of the opinion that in such cases definite results have to be obtained within six months to be of any significance regarding the value of the drug which is being used. Because of the difficulty of assessing the activity of the drug in neural cases, and also because the possibility of producing sulphone resistant *M. leprae* cannot be excluded, it is advocated that at present, except for experimental purposes, the sulphones should not be administered as a routine in neural cases.

While a significant advance has been made in the therapy of leprosy, it behoves us to remember that the search must be continued for still more effective chemotherapeutic agents, and that when the bacterial battle for leprosy has been won we may still be a long way from solving the problems of relief, prevention of deformity and amelioration of the ravages of the disease. Therefore the orthopedic surgeon, the physiotherapist, and the social welfare worker all have tasks which will continue to exist long after the therapeutic problem has been satisfactorily solved. In any disease, and particularly in leprosy, it is perilous to have a narrow view; and to attempt to contain one's interest within a single sector, ignoring pathology, bacteriology, orthopedic surgery and social welfare, will only lead to disaster. If we are to contribute effectively to the final elimination of this disease our vision must include the whole field, and not be the myopic vision of one who only concentrates on the search for a specific cure for leprosy. —R. G. COCHRANE.

<sup>10</sup> DE SOUZA LIMA, L. Present status of sulfone therapy at the Padre Bento sanatorium. THE JOURNAL 16 (148) 127-137.