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EDITORIALS

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THE ADMINISTRATION OF DIAMINODIPHENYL SULFONE AND ITS DERIVATIVES BY THE ORAL AND PARENTERAL ROUTES, WITH AN ASSESSMENT OF THEIR RELATIVE VALUES

Sulfone therapy of leprosy, first introduced fifteen years ago by Faget and associates,[1] is one of the triumphs of modern medicine and holds pride of place in the treatment of this disease. These drugs have torn the mask of terror from the face of leprosy. The problem which has to be considered is not the efficacy of sulfone therapy, but the best way to administer it, so that as many persons as possible who suffer from the disease can be reached by effective treatment. Diaminodiphenyl sulfone (DDS) and its derivatives will continue to be the standard of treatment until such time as a more effective, more economical, and less toxic drug is discovered. It is, however, timely to bring under discussion the whole question of mass treatment of leprosy, and the best methods by which to administer the parent drug.

When diaminodiphenyl sulfone was first used at the end of 1946, and subsequently on a much larger scale in 1949,[2] oral administration was rejected on account of warning given with regard to its toxicity.

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[1] FAGET, G. H., POGGE, R. C., JOHANSEN, F. A., DINAN, J. F., PREJEAN, B. M. and ECCLES, C. G. The promin treatment of leprosy. A progress report. Publ. Hlth. Rep. **58** (1943) 1729-1741.

[2] COCHRANE, R. G., RAMANUJAM, K., PAUL, H. and RUSSELL, D. Two-and-a-half years' experimental work on the sulphone group of drugs. Leprosy Rev. **20** (1949) 4-64.

Following the work in Madras, Muir ([3]), and then Lowe ([4]), experimented with the administration of diaminodiphenyl sulfone by the oral route, which has now become the method of choice in most parts of the world. The French workers, however, Floch ([5, 6]) and Laviron ([7]) in particular, have re-investigated the whole question of injectable suspensions of DDS, and in general they and the Belgian workers favor parenteral administration, whereas those working in most of the other countries prefer the oral route. In the United States, at the U. S. Public Health Service Hospital at Carville, Promin intravenously and Diasone orally are still in use.

Intravenous injections, however, are not practical where mass treatment is contemplated, and particularly when the routine treatment has to be undertaken by the paramedical personnel. Further, the cost of a drug such as Diasone is prohibitive. Therefore, the comparable efficacy of these two drugs in the therapy of leprosy need not be considered. I shall, therefore, confine this review to the sulfone drugs which are more economical in use and more simple to administer, for example, oral DDS, injectable sulfones, and injectable Sulphetrone.

Dapsone.—Muir [3] first administered DDS (dapsone) by the oral route. He made a suspension of the powder in water and administered it by drops. Following his work Lowe, [4] in Nigeria, began giving DDS in the form of a tablet. The initial dosage tended to be too high, and considerable toxicity was the experience of the early workers. When Lowe finally settled on lower dosages, and particularly twice weekly rather than daily, toxicity was reduced very greatly. [8] The oral route is the method of choice in the majority of leprosaria and dispensaries.

The advantages of the oral route are that the drug is easy to administer and can be most conveniently given in out-patient dispensaries,

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[3] MUIR, E. Preliminary report on 4:4′ diaminodiphenyl sulfone (DDS) treatment of leprosy. Internat. J. Leprosy **18** (1950) 299-308.

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

[5] FLOCH, H. and GELARD, A. M. Une injection intramusculaire de 1 gr. 80 de diaminodiphényl-sulfone peut donner une sulfonémie satisfaisante pendant un mois. Arch. Inst. Pasteur Guyane Française Publ. No. 340, 1954.

[6] FLOCH, H. and LECUILLER, A. Devenir de la diaminodiphénylsulfone en administration experimentale à des cobayes dans l'organisme de ces derniers. Bull. Soc. Path. exot. **46** (1953) 10-15.

[7] LAVIRON, P., LAURET, L. and JARDIN, G. Résultats après trois ans de traitement de la lèpre par les injections espacées de DDS dans le chaulmoograte d'éthyle. Méd. Tropicale **14** (1954) 69-71.

[8] LOWE, J. and DAVEY, T. F. Four years' experience of sulphone treatment of leprosy. Trans. Roy. Soc. Trop. Med. & Hyg. **44** (1950-1951) 635-662.

because no elaborate preparation is necessary as is the case when a drug is injected. The disadvantages are that it is difficult to supervise the administration of the drug when the number of patients who attend for out-patient treatment runs into several thousands, for the temptation to sell the drug illicitly is very great, and in certain countries the black market in sulfone pills is not inconsiderable. Secondly, while the toxicity factor has been reduced very greatly since the introduction of the small dose and the longer period taken to reach the maximum dose, toxicity is not unknown as a result of overdosage. Toxicity with the parenteral administration of DDS is extremely rare in the dosages given.

Injectable sulfones.—The following preparations of DDS are used in treatment by injections: DDS suspended in vegetable oils, for example arachis (peanut) oil, coconut oil, and chaulmoogra oil, or the esters of chaulmoogric acid. An aqueous suspension of DDS has also been recommended. Undoubtedly, where it is obtainable and reasonably cheap, coconut oil, as used by Molesworth[9] in Malaya, is the most practical agent in which to suspend DDS. Where this is not obtainable peanut oil may be used, or the aqueous suspension.

The French workers in Africa [7] claim that the best suspending agent is ethyl esters of chaulmooga oil. My experience is that this suspension is painful, which is a drawback. Other French workers, particularly Floch,[10] have emphasized the importance of using a suspending agent which will have the greatest retard effect; but the experience of Indian workers [11] and of Molesworth indicates that both coconut oil and arachis oil are effective, and these are certainly more practical media, for DDS suspensions can be made up in leprosy institutions and therefore these two suspending agents are most economical and relatively free from pain.

With regard to the aqueous suspension of DDS as recommended by Williams [12] of Kuluva, Uganda, he states that it is necessary to use the Avlosulfone tablets (I.C.I.), for these more readily go into suspension than other tablets of the same remedy. A domestic shaker called "Quick-Mix" is used, and two tablets of Avlosulfone are crushed up with 1 cc. of saline and the whole is shaken and results in a very fine suspension of DDS. The method appears to be entirely satisfactory.

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[9] MOLESWORTH, B. D. and NARAYANASWAMI, P. S. The treatment of lepromatous leprosy with 4:4'-diaminodiphenyl sulfone in oil. Findings in 100 cases treated for one year. Internat. J. Leprosy **17** (1949) 197-208.

[10] FLOCH, H. and GELARD, A. M. Utilisation de la DDS-retard en fonction de la grosseur des cristaux de la suspension. Bull. Soc. Path. exot. **47** (1954) 35-40.

[11] ROY, A. T. Suspension of diaminodiphenylsulphone in leprosy. Leprosy Rev. **23** (1952) 73-79.

[12] WILLIAMS, E. H. and WILLIAMS, P. H. The story of Kuluva. Leprosy Rev. **24** (1953) 132-138.

No blood levels, however, have been done, and, therefore, one cannot say that an adequate blood level of DDS is maintained. The results of treatment, however, are satisfactory.

In addition to these there are two other injectable sulfone preparations, one of which is in more general use. They are soluble Avlosulfone (I.C.I.) and aqueous Sulphetrone. Davey [13] has shown that soluble Avlosulfone is a satisfactory preparation, and that, compared with oral DDS, it is considerably less reactive. But this preparation is more expensive, and therefore less practical, than straightforward suspension of DDS in oily or watery media.

Parenteral Sulphetrone in a 50 per cent solution was first used in Madras,[2] and has proved a valuable alternative to DDS treatment. The advantages over suspension of DDS are: first, the dosage is much more easily regulated if the case shows a tendency to reactions; secondly, the number of reactions which are precipitated is far less than with any of the supensions of DDS; thirdly, it is easy to administer, and there is no likelihood of any residual unabsorbed masses which sometimes occur with oily suspensions of DDS, particularly when arachis oil is used. It has been shown [2] that Sulphetrone does not break down to the parent substance, and, as the therapeutic dose is only 1 cc. twice a week, the cost is only slightly in excess of oral DDS and hardly more expensive than suspensions of DDS in oily media. The solution is easily prepared and remains stable for many months.

These, then, are the preparations of DDS which are used for parenteral injections, and an increasing number of workers are stressing the advantages of parenteral DDS over oral remedies. The French workers maintain that by using their preparations of parenteral DDS, not only is the retard action more effective but the blood levels keep at a more constant level, and therefore there is no need to give injections more often than once a fortnight. Ramanujam,[14] and Roy, [11] have put forth evidence that parenteral DDS is not only much less reaction producing, but that the results of treatment are better and the relapse rate is decidedly lower.

One disadvantage of parenteral DDS over oral remedies is that arrangements have to be made for injections, and there is always a risk that abscesses may be produced. Furthermore, it increases the cost of treatment because of the necessity for the purchase of syringes and apparatus for injections, and, where non-medical personnel is used, it may increase the danger of the workers not only setting up their own practice in injecting DDS, but of using their syringes for injecting other remedies, such as penicillin, and therefore it encourages unqualified practitioners. On the other hand there is evidence to show

[13] DAVEY, T. F. Experience with "Avlosulfon" soluble. Leprosy Rev. **27** (1956) 6-18.

[14] RAMANUJAM, K. Comparison of oral and parenteral DDS treatment. Internat. J. Leprsoy **24** (1956) 196-197 (correspondence).

that in certain countries the black market in sulfone tablets is not inconsiderable, and it is claimed that there is less likelihood of extensive illicit administration of sulfones when they are given by the parenteral route rather than orally.

The fact remains, however, that DDS and its preparations are now established as the routine treatment of leprosy, and workers have to take into consideration the method which is likely to be the most practical in the area under their administration, keeping in mind the principle that all who have leprosy should receive treatment. Personally, I prefer oral remedies in in-patient institutions, where the administration of tablets can be controlled and where signs of intolerance to the drug can be recognized at once. It must, however, be pointed out that a certain number of cases will show intolerance even to parenteral DDS, and therefore in these cases the alternative drug which I recommend is an aqueous solution of Sulphetrone injected intramuscularly or deep subcutaneously.

In conclusion, I should like to pay particular tribute to the work of the late Dr. John Lowe, who demonstrated more than anyone else the practicability of using DDS, the parent sulfone.

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