Diaminodiphenyl sulfone, the so-called mother substance of the familiar sulfone drugs, is undoubtedly becoming increasingly important in the therapy of leprosy. Long since recognized as active but shelved for a full decade after its first clinical trials because of a reputation of excessive toxicity, it has been used for some years in England in veterinary medicine, and those who have had most experience in that field are convinced—as are others—that it is the active element in the derivatives which have been used.[1]

The first trial of DDS in leprosy arose from the need of a form of sulfone more rapidly effective than the derivatives in use. When visiting England in 1946, Cochrane learned of its use in veterinary medicine and was encouraged to try it out in patients. Beginning on a small scale early in 1947 he injected it suspended in peanut oil, and as a result the Committee on Therapy of the Havana Congress mentioned it as one of the drugs needing further investigation. Before that, at Cochrane's suggestion, Molesworth and associates in Malaya put 100 cases under treatment by his method, but in smaller dosage and suspended in coconut oil, which gives less trouble from non-

[1] FRANCIS, J. and SPINKS, A. Antibacterial action and metabolism of five sulphones. British J. Pharmacol. & Chemother. **5** (1950) 565-583.

absorption. After one year they reported [2] very good results and relatively little trouble on account of toxicity.

In the meantime, quite independently if from the same ultimate source, the matter was brought to Lowe's attention, and when he started work in Nigeria late in 1947 he put a few cases under treatment; but—on advice, it is understood, of Dr. E. Muir—he decided to administer it by mouth. In the first report of the work started there [3] one page is devoted to a small preliminary trial. Striking results had been seen, and it was not long before this drug became Lowe's major interest.

The use of this medicament in human cases was at first empyrical, but—apart from work with cattle—there have been animal studies of its pharmacology. M. I. Smith and associates [4] reported its metabolic fate in rabbits; their findings cannot be readily summarized. Titus and Bernstein [5] studied the blood levels of DDS in animals given various sulfones from the point of view of the "frequent assumption" that they act by virtue of that element; they found among other things that when DDS itself was given by mouth to dogs it was more completely absorbed than any of the derivatives used. Interesting results are to be found in the article of Francis and Spinks referred to.[1]

The first studies of this nature on patients under treatment were made by Michael Smith, who showed [6] that DDS is extremely well absorbed from the gut, far better than either of the derivatives used, and is slowly but almost completely excreted in the urine, and he suggested adjusting the dosage to give a blood level comparable in terms of chemical equivalents with that obtained when using the derivatives. He also reported further studies regarding the break-down of the derivative com-

---

[2] MOLESWORTH, B. D. and NARAYANASWAMI, P. S., with SIMPSON, I. A. 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) 197-210.

[3] LOWE, J. and SMITH, M. The chemotherapy of leprosy in Nigeria. Internat. J. Leprosy **17** (1949) 181-195.

[4] SMITH, M. I., JACKSON, E. L., CHANG, Y. T. and LONGENECKER, W. H. Metabolic fate of 4,4'-diaminodiphenyl sulfone (DDS) in the rabbit and its isolation from urine. Proc. Soc. Exper. Biol. & Med. **71** (1949) 23-25; (*abstracted* I. J. L. **17** (1949) 356).

[5] TITUS, E. and BERNSTEIN, J. The pharmacology of the sulfones. Ann. New York Acad. Sci. **52** (1949) 719-728; (*abstracted* I. J. L. **18** (1950) 293).

[6] SMITH, M. A pharmacological study of three sulfones. Lep. Rev. **20** (1949) 77-88; (*abstracted* I. J. L. **18** (1950) 122).

pounds to DDS, and toxic effects.[7] Recently Dharmendra and associates [8] have made an extensive pharmacological investigation of DDS to determine the best mode of administration and the best dosage. It seems to be agreed that about 90 per cent of the dose given by mouth is absorbed and thus made available, far more than any of the derivatives so administered.

The number of informative reports of clinical trials is not large, but it is increasing rapidly. Lowe's principal one to date [9] reviews the matter thoroughly. He had found that improvement was more rapid than with the other sulfones used, and that the cost was very low. At that time he was using 300 mgm. a day, but more recently [10] he has reported that 100 mgm. daily is usually enough to produce good results, although he recommends around 1 gm. a week as the maximum—either 200 mgm. six times a week, or 300 mgm. three times a week, or 500 mgm. twice a week. Such dosage is recommended [11] for institutions where medical supervision is limited, and the last one especially for outpatient treatment. He has also shown [12] that DDS is effective in tuberculoid cases.

Floch and Destombes,[13] in French Guiana, used DDS ("1358F") by both the oral and the intramuscular routes, and found that in either case 200 mgm. a day is well tolerated. They regard this drug as having a "practical superiority" over the derivatives. An interesting attempt has been made by Schneider [14] to meet field conditions in Africa by using 1.25 gm. suspended

---

[7] SMITH, M. *Idem.* Part. II. Hydrolysis and the specific toxic phenomena. Part III. The specific toxic phenomena. Lep. Rev. **20** (1949) 128-134 and **21** (1950) 17-29; (*abstracted* I. J. L. **18** (1950) 553 and 554).

[8] DHARMENDRA, CHATTERJEE, K. R. and BOSE, R. Diamino-diphenyl-sulphone (DDS) in the treatment of leprosy; pharmacological aspects. Lep. India **22** (1950) 174-201. (For the conclusions, see also I. J. L. **18** (1950) 533, correspondence).

[9] LOWE, J. Treatment of leprosy with diamino-diphenyl sulphone by mouth. Lancet **1** (1950) 145-150; (*abstracted* I. J. L. **18** (1950) 549).

[10] LOWE, J. Dosage of diamino-diphenyl sulphone. Lancet **2** (1950) 36-37; (*abstract* in this issue).

[11] LOWE, J. Sundry experiences in the chemotherapy of leprosy. Internat. J. Leprosy **19** (1951) 15-21.

[12] LOWE, J. The sulfone treatment of tuberculoid leprosy. Internat. J. Leprosy **18** (1950) 457-468.

[13] FLOCH, H. and DESTOMBES, P. Traitement de la lèpre par la "sulfone-mère" (diamino-diphenyl-sulfone). Internat. J. Leprosy **17** (1949) 367-377; *also* Bull. Soc. Path. exot. **42** (1949) 434-439 and elsewhere.

[14] SCHNEIDER, J. Etat actuel de l'expérimentation de nouvelles therapeutiques de la lèpre. (Thiosémicarbazone—Suspensions huileuses de DDS.) Rev. brasileira Leprol. **18** (1950) 186-205.

in chaulmoogra oil injected weekly or even biweekly. Floch and associates at first [15] reported unfavorably on this method, pointing out especially that with biweekly injections the dosage was clearly insufficient. More recently, however, they have reported [16] favorably on weekly injections, finding the chaulmoogra suspension satisfactory but of no advantage from the chaulmoogra element because of the small dosage, and recommending as the preferred menstruum 2 per cent agar in saline.

Muir,[17] at first using only the oral route, treated 96 cases with good results. Recently [18] he has reported his further experience, saying that DDS is very effective in small amounts, so given, not more toxic than its derivatives. With regard to effectiveness, it may be given orally or by injection, but for conditions such as those in India he prefers (subcutaneous) injection. Dharmendra and associates,[8] however, have decided in favor of the oral route; and, to reduce toxic effects, they recommend a dosage of 100 mgm. a day, or at most in special cases 200 mgm., in either case to be given in two divided doses rather than in a single dose.

Cochrane has remained cautious. After his first trials,[19] in which he treated 11 cases with a maximum dosage of 1.25 gm. of the substance injected twice a week, he said that DDS is the most rapidly acting and probably the most potent antileprosy remedy, but that it could not be recommended for general use until a less toxic dosage should be arrived at. Shortly, it appears, he found that 1.5 gm. a week was better tolerated. Recently,[20] he has recommended a maximum of 600 mgm. a week (100 mgm. per day for six days of the week, or 300 mgm. twice a week)

---

[15] FLOCH, H., DESTOMBES, P. and LECUILLER, A. Sur l'emploi de la sulfone-mère en suspension huileuse. Bull. Soc. Path. exot. **44** (1951) 103-110.

[16] FLOCH, H., LECUILLER, A. and DESTOMBES, P. La sulfone-mère-retard en eau physiologique gélosée permet de ne pratiquer, pour le traitement des lépreux, qu'une injection intramusculaire par semaine. Inst. Pasteur Guyane et Terr. Inini, Publ. No. 228, April 1951.

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

[18] MUIR, E. Bacteriological changes under DDS treatment of leprosy. Lep. India **23** (1951) 116-126. (To be reprinted.)

[19] COCHRANE, R. G., RAMANUJAM, K., PAUL, H. and RUSSEL, D. Two-and-a-half years' experimental work on the sulphone group of drugs. Lep. Rev. **20** (1949) 4-64; (*abstracted* I. J. L. **17** (1949) 354).

[20] COCHRANE, R. G. Chemotherapy in leprosy. Practitioner **166** (1951) 373-381; (*abstract* in this issue).

unless adequate supervision is possible. He writes [21] that in India even 100 mgm. a day is toxic for many patients, and that in the forthcoming issue of *Leprosy Review* there is a report of four deaths of patients who had been receiving 200 mgm. per day. He therefore holds that the use of DDS is not practical for the average practitioner or the outpatient clinic. Besides the danger of misuse by the patients resulting in either insufficient or excessive and toxic dosages, he holds, there is also the consideration that a black market in the drug may arise. It is obvious that if the drug could be used only for hospitalized patients —and of them only those in well-supervised institutions—it could be given to only a relatively small proportion of those who need treatment. Dharmendra, however, has registered a contrary opinion, holding DDS to be safe for outpatient treatment of suitably selected patients.[22]

Much has been made of the point that DDS is highly economical. As said, Lowe has stated that the cost is about one-twentieth that of the usual proprietary sulfones in the usual doses by mouth. Kellersberger has written [23] that the cost is about $1 per patient per year against up to $30 for the other drugs as usually given, or at best $4 for sulphetrone by injection. But Cochrane points out [21] that at 200 mgm. per day the cost would be around 15s. per year, without considering the iron and yeast that should be given, whereas sulphetrone given by injection in the usual dosage (3.5 gm. per week) costs approximately 15s. to 20s., and that may be materially reduced since there is evidence that much smaller dosage is effective by that route of administration. Dharmendra [22] has given other figures, in Indian currency.

Curiously, DDS is not as widely available as might be expected. The main source is the Imperial Chemical (Pharmaceuticals), Ltd., of England, who market it under the trade name Avlosulfon; and in many places customs duties add materially to its cost. It appears [24] that it is also put out by the Bengal Immunity Co., of Calcutta, as Diphone. In France it is available in tablets—said to contain iron—under the name Disulone. On the understanding that 4,4′-diaminodiphenyl sulfone is used as the starting point of the derivatives, except

---

[21] COCHRANE, R. G. Personal communication.

[22] [EDITORIAL] The place of diamino-diphenyl-sulfone in the mass treatment of leprosy. Lep. India **23** (1951) 113-114.

[23] KELLERSBERGER, E. R. Personal communication.

[24] DHARMENDRA. The present status of sulfones in the treatment of leprosy. Indian Med. Gaz. (1950) 348-360; (*abstracted* I. J. L. **19** (1951) 98).

promizole, we recently inquired whether it could be obtained in the United States in a form which could be used for treatment, but Dr. J. A. Doull, who inquired into the matter, was told that it is not made in that country—that it is not used as the starting substance in the manufacture of diasone and promin.

Whatever the situation with regard to tolerance in India—and perhaps also in China, for it is said that there, too, more toxic effects are seen than is desirable—the use of DDS is being rapidly extended in Africa. In Nigeria, according to Lowe,[25] there were some 2,500 patients under treatment in July 1950, and the number was being rapidly increased because of change-over from other drugs. In October, he reported, over 5,000 cases were on the drug, and he expected the number to reach 10,000.

Now there comes word [23] that the American Leprosy Missions, Inc. has discontinued supplying to its stations the sulfone derivatives previously used, because DDS is just as efficient and much cheaper. The Mission to Lepers (London), has also made a move in that direction, having issued a permissive memorandum authorizing the use of DDS in its institutions where there is a resident medical officer and necessary other facilities, without necessarily excluding the use of other drugs.[26] This shift of emphasis is ascribed largely to recent experience in Nigeria, but also in part because of a recommendation by Muir to the Missions to Lepers with respect to its leprosaria there.[27] It is also said that Chaussinand, as advisor on leprosy to the government of France, has recommended that DDS—in the form prepared in France—be used in all of the French colonies.

Here has developed a situation without parallel, the wholesale adoption of a potent but highly toxic drug, in use for a relatively short period and still under active discussion regarding dosage and route of administration, to be used as the standard drug under a wide variety of conditions, mostly where medical supervision cannot be regarded as close and to a great extent in outpatient practice. The outcome will be of great interest to all who are concerned with the treatment of leprosy patients. It is to be hoped that arrangements will be made for the frank reporting of the results of this large-scale experiment, with respect to untoward effects as well as favorable results. —H. W. WADE

---

[25] LOWE, J. Personal communication.

[26] MILLER, A. D. Personal communication.

[27] Dr. Muir has also recommended, in a report which will be reviewed in our next issue, the use of DDS in the leprosaria of Greece.