Patient Compliance with Dapsone Administration in Leprosy[1]

Aspects of dapsone are reviewed in their historical context. After a description of early history, special attention is paid to the search for the optimum dose of dapsone in leprosy. The present problem of sulfone resistance has apparently closed the discussion about low doses and has focused attention on patient compliance with dapsone administration. This leads to the need of simple methods for detecting sulfones in body fluids.

EARLY HISTORY OF DAPSONE IN LEPROSY

Dapsone, A New Antibacterial Agent

Coccal infections. Domagk's discovery of the antibacterial properties of prontisil (2,4-diaminoazo-benzene-4'-sulfonamide) in 1935[2] initiated a new era in chemotherapy. In the same year Tréfouël and associates found that p-aminobenzenesulfonamide (sulfanilamide) was equally active[3], and soon a search started for substances of broader therapeutic spectrum and lower toxicity. Buttle and colleagues were the first to turn their attention to 4,4'-diaminodiphenyl sulfone (dapsone, DDS), synthesized in 1908 by the dye researchers, Fromm and Wittmann[4]. In 1937, they reported dapsone to be 100 times more effective than sulfanilamide in streptococcal infections in mice[5]. They found the drug alsc effective in staphylococcal infections and considerably better than sulfanilamide in prolonging the lives of mice infected with pneumococci. Its therapeutic effect was more persistent. Though in mice dapsone was 25 times as toxic as sulfanilamide, in rabbits or monkeys it was not more toxic than the latter. In the same paper they reported that after a single dose of 300 mg DDS taken by Buttle himself, the blood had definite antibacterial properties. This experiment caused no side effects apart from a very small quantity of methemoglobin 5 hours after administration. A subsequent therapeutic trial in human beings with acute infections was revealed only many years later by personal communications of Buttle to Lowe[6] and Doull[7]. Doses of the order of 1–2 g a day were given but because of the rapid production of methemoglobinemia and other toxic effects, the treatment was soon abandoned.

Most authors reviewing the sulfone history[7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17] mention the paper of Fourneau and colleagues[18], pub-

[1] This essay was originally prepared by Dr. Huikeshoven in partial fulfillment for the requirements of Ph.D.

[2] Domagk, G. K. Prontisil. Dtsch. Med. Wochenschr. **61** (1935) 250–253.

[3] Tréfouël, J., Tréfouël, J., Nitti, F. and Bovet, D. Activité du p-amino-phényl-sulfamide sur les injections streptococciques experimentales de la souris et du lapin. C. R. Soc. Biol. (Paris) **120** (1935) 756–758.

[4] Fromm, E. and Wittmann, J. Derivate des p-nitrothiophenols. Ber. Dtsch. Chem. **41** (1903) 2264–2273.

[5] Buttle, G. A. H., Stephenson, D., Smith, S., Dewing, T. and Foster, G. E. The treatment of streptococcal infections in mice with 4:4'diamino-diphenylsulfone. Lancet **1** (1937) 1331–1336.

[6] Lowe, J. Treatment of leprosy with diaminodiphenyl sulphone by mouth. Lancet **1** (1950) 145–150.

[7] Doull, J. A. Sulphone therapy of leprosy. Background, early history and present status. Int. J. Lepr. **31** (1963) 143–160.

[8] Buttle, G. A. H., Dewing, T., Foster, G. E., Gray, W. H., Smith, S., and Stephenson, D. The action of substances allied to 4:4'-diaminodiphenylsulphone in streptococcal and other infections in mice. Biochem. J. **32** (1938) 1101–1110.

[9] Rist, N., Bloch, F. and Hammon, V. Action inhibitrice du sulfamide et d'une sulfone sur la multiplication *in vitro* and *in vivo* du bacille tuberculeux aviaire. Ann. Inst. Pasteur **64** (1940) 203–237.

[10] Coggeshall, L. T., Maier, J. and Best, C. A. The effectiveness of two new types of chemotherapeutic agents in malaria. JAMA **117** (1941) 1077–1081.

[11] Floch, H. and Destombes, P. Traitement de la lèpre par la "sulfone-mère" (diamino-diphenyl-sulfone). Int. J. Lepr. **17** (1949) 367–377.

[12] Rist, N. and Cottet, J. Les sulfones en thérapeutique. Presse Méd. **52** (1949) 743–745.

[13] Francis, J. and Spinks, A. Antibacterial action and metabolism of five sulphones. Br. J. Pharmacol. **5** (1950) 565–583.

[14] Lowe, J. Studies in sulphone therapy. Lepr. Rev. **23** (1952) 4–29.

[15] Tréfouël, J. Priority re oral DDS therapy. Int. J. Lepr. **30** (1962) 202–204 (correspondence).

[16] Bushby, S. R. M. Chemotherapy. In: *Leprosy in Theory and Practice*. 2nd ed. Cochrane, R. G. and Davey, T. F., eds. Bristol: John Wright & Sons Ltd., 1964, 344–370.

[17] De Gowin, R. L. A review of therapeutic and hemolytic effects of dapsone. Arch. Int. Med. **120** (1967) 242–248.

[18] Fourneau, E., Tréfouël, J., Nitti, F., Bovet, D. and Tréfouël, J. Action antistreptococcique des derivés sulfurés organiques. C. R. Acad. Sci. **204** (1937) 1763–1766.

lished only two days after that of Buttle's group, as an equally valid starting point of dapsone therapeutic trials. However, this paper describes work with the ten times less active 4,4′-dinitrodiphenyl sulfone, referring only indirectly to DDS. It was four months later when, in another paper, they reported the superior activity of DDS itself against streptococci in mice[19].

In 1938, only one year after Buttle's first publication, Feinstone and co-workers[20] concluded their experimental work with DDS in streptococcal, pneumococcal, meningococcal and staphylococcal infections in mice with the statement: "Its toxicity, in our opinion, precludes its use in human beings." However, their results were equal to those of Buttle's group and they did not really search for the minimum effective dose, the lowest dose used by them being 0.1 g DDS/kg mouse. Contrary to their conclusion that it should not be used in man, they decided in the same year to test its efficacy in four cases of subacute bacterial endocarditis, setting their doses at a somewhat lower level than they had found to be effective in mice, based on a weight for weight comparison. They were scared off within a few days of treatment because of severe anemia, and they did no more with the compound. This experiment done in 1938 was revealed only in 1950[21].

Also in 1938 Bauer and Rosenthal[22] found that the therapeutic index of DDS (maximum tolerated dose/minimum effective dose) against streptococci in mice was 6 as compared to 3.3 for sulfanilamide. Yet they found it desirable to obtain derivatives with lower toxicity without a corresponding decrease in therapeutic action.

Tuberculosis. The next year the first experiments of Rist and co-workers with DDS in tuberculosis were published. They reported that DDS exerted a 10 times stronger inhibition on avian tuberculosis than sulfanilamide[23] and that DDS stopped the multiplication of *Mycobacterium avium* in rabbits and guinea pigs[24]. In further experiments by this group of workers the superiority of DDS against *M. avium* both *in vitro* and *in vivo* was clearly shown[9]. Smith and colleagues found the same for its activity against experimental bovine and human tuberculosis[25], but they concluded that the toxicity and the specificity of the compound made "the search for more effective and less toxic derivatives a promising field of investigation." In 1944 Feldman and coworkers[26] largely confirmed the effectiveness of DDS in experimental tuberculosis in guinea pigs. Although they did not find it excessively toxic in the dose used, they too suggested "modifying DDS to obtain a compound more suitable for clinical application."

However, at this time streptomycin was isolated which could eradicate tuberculosis[27], and work with sulfones which only arrested this disease was soon abandoned[28].

Veterinary medicine. Meanwhile veteri-

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[19] Fourneau, E., Tréfouël, J., Tréfouël, J., Nitti, F. and Bovet, D. Rapport entre la constitution chimique et l'activité thérapeutique antimicrobienne des dérivés organiques du soufre: phényl-sulfamides, diphénylsulfures, diphénylsulfones. Bull. Acad. Med. **118** (1937) 210–217.

[20] Feinstone, W. H., Bliss, E. A., Ott, E. and Long, P. H. Observations concerning the toxicity, absorption and therapeutic effect of sulphanilamide and certain related organic sulphur-containing compounds in experimental infections in mice. Bull. Johns Hopkins Hosp. **62** (1938) 565–592.

[21] Long, P. H. (Early experience with DDS in man). Int. J. Lepr. **18** (1950) 247 (correspondence).

[22] Bauer, H. and Rosenthal, S. M. Studies in chemotherapy. VII. Some new sulphur compounds active against bacterial infections. Public Health Rep. **53** (1938) 40–49.

[23] Rist, N. Action du p-aminosulfamide et de la p-diaminodiphénylsulfone sur la culture des bacilles tuberculeux des Mammifères et des Oiseaux. C. R. Soc. Biol. **130** (1939) 972–975.

[24] Rist, N., Bloch, F. and Hamon, V. Action inhibitrice du p-aminophényl-sulfamide et de la p-diaminodiphénylsulfone sur la multiplication *in vivo* d'un bacille tuberculeux aviaire. C. R. Soc. Biol. **130** (1939) 976–980.

[25] Smith, M. I., Emmart, E. W. and Westfall, B. B. The action of certain sulfonamides, sulfones and related phosphorus compounds in experimental tuberculosis. J. Pharmacol. Exp. Ther. **74** (1942) 163–174.

[26] Feldman, W. H., Hinshaw, H. C. and Moses, H. E. The effects on experimental tuberculosis of 4,4′-diaminodiphenylsulfone. Am. J. Med. Sci. **207** (1944) 290–305.

[27] Schatz, A. and Waksman, S. A. Effect of streptomycin and other antibiotic substances upon *Mycobacterium tuberculosis* and related organisms. Proc. Soc. Exp. Biol. Med. **57** (1944) 244–248.

[28] Smith, M. I., Jackson, E. L. and Bauer, H. Evaluation of the sulfones and streptomycin in experimental tuberculois. Ann. N.Y. Acad. Sci. **52** (1949) 704–718.

narians were really optimistic about the effect of DDS on streptococcal infections. McEwen and colleagues reported in 1941[29] that it quickly improved the clinical condition of cattle suffering from mastitis without toxic symptoms. It appeared to possess "virtues equal to those of sulphanilamide," but it was free from the "objectionable properties of the latter." Blood levels as high as 60 μg/ml were well tolerated. It is this work with cattle that finally led to the first clinical trials with the parent sulfone, DDS, in leprosy.

First, however, some of the substituted sulfones would prove to be active against this much feared disease.

Substituted Sulfones

DADDS. The first reports of the clinical use of a sulfone in man dealt with a disubstituted sulfone. In 1937 Heitz Boyer and co-workers[30] and Palazzoli and Bovet[31] successfully used p-diacetylaminodiphenyl sulfone (DADDS) in the treatment of gonorrhea. The effectiveness of DADDS in experimental pneumococcal and streptococcal infections was shown in the same period by several groups of workers[8,19,22,32]. In 1941 it was also successfully tried in experimental malaria[10], but no favorable effect could be obtained with DADDS in experimental tuberculosis[25].

Similar early experiments were done with 4,4′-dinitrodiphenyl sulfone[5,18], disodium formaldehydesulphoxylate-diaminodiphenylsulfone[22], a benzylidene derivative of DDS[8] and many more compounds derived from DDS[8]. Often a promising activity was found against streptococcal or pneumococcal infections, though none of these derivatives was as effective as the parent sulfone, DDS, itself.

Promin. Special mention should be made of Promin (p,p′-diaminodiphenylsulfone-N,N′-di[dextrose sodium sulfonate]), the first sulfone that would eventually be used in leprosy. In 1939 a report was published of a trial of Promin in experimental pneumonia in mice by Greey and colleagues[33]. Clinical trials in pneumonia and other acute infections were carried out in 1939–1941 by various workers. The drug was found to be toxic when given orally but was well tolerated by the parenteral route. Thus Toomey and Roach reported in 1941[34] intravenous administration of Promin to 154 patients with relatively few untoward reactions. In the same year Coggeshall and colleagues showed that Promin had a definite effect on naturally acquired human malaria infections[10].

Tuberculosis studies using Promin were commenced in 1940 by Feldman and coworkers. The drug was shown to inhibit the development of experimental tuberculosis in guinea pigs[35] and to restrain the disease and produce retrogressive changes in the lesions of infected animals[36]. Subsequently Promin was employed in the treatment of more than 75 patients who had various infections, including pneumonia and tuberculosis. The drug was administered orally, subcutaneously, intramuscularly, and intravenously. After oral administration serious hemolytic anemia, cyanosis of striking intensity, and some subjective complaints were noted. These symptoms were largely absent when Promin was given parenteral-

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[29] McEwen, A. D., Pizer, N. H. and Paterson, J. D. Preliminary trials on the administration of sulphonamide E.O.S. and of 4:4′-diaminodiphenylsulphone to normal cattle and to cattle affected with streptococcal mastitis. Vet. Rec. **53** (1941) 429–436.

[30] Heitz-Boyer, Nitti, F. and Tréfouël, J. Note préliminaire sur l'action de la paradiacétylaminodiphénylsulfone (1399F.) dans la blennorragie. Bull. Soc. Fr. Dermatol. Syphiligr. **44** (1937) 1899.

[31] Palazzoli, M. and Bovet, D. Action de la di(paraacétylaminophényl) sulfone (1399F.) dans les urétrites gonococciques aiguës et chroniques. Bull. Soc. Fr. Dermatol. Syphiligr. **44** (1937) 1900–1910.

[32] Fourneau, E., Tréfouël, J., Tréfouël, J., Nitti, F. and Bovet, D. Chimiothérapie de l'infection pneumococcique par la di-(p-acétylaminophényl)-sulfone (1399F). C. R. Acad. Sci. **205** (1937) 299–300.

[33] Greey, P. H., McLaren, D. B. and Lucas, C. C. Comparative chemotherapy in experimental pneumococcal infections. Can. Med. Assoc. J. **40** (1939) 319–324.

[34] Toomey, J. A. and Roach, F. E. Promin in the treatment of some acute infections. J. Pediatr. **18** (1941) 1–5.

[35] Feldman, W. H., Hinshaw, H. C. and Moses, H. E. Effect of promin (sodium salt of p,p′-diamino-diphenylsulfone-N,N′-didextrose sulfonate) on experimental tuberculosis. A preliminary report. Proc. Staff Meet. Mayo Clin. **15** (1940) 695–699.

[36] Feldman, W. H., Hinshaw, H. C. and Moses, H. E. The treatment of experimental tuberculosis with promin (sodium salt of p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate). A preliminary report. Proc. Staff Meet. Mayo Clin. **16** (1941) 187–193.

ly. Yet patients preferred the oral route because the symptoms noted were less uncomfortable than the distress produced by injections[37]. A remark of Myers' in an abstract of discussion, added to the last publication, illustrates the difficult circumstances in which this first clinical work had to be carried out: "I should like to suggest that the physicians of this country (USA) allow Drs. Hinshaw and Feldman to proceed unmolested."

Smith and colleagues confirmed in 1942 the tuberculostatic action of Promin, but they found it 10 times less active than DDS[25].

Active nucleus. It is interesting to note that, starting from 1938, workers already realized that the parent sulfone was likely to be both the therapeutic and the toxic substance in the disubstituted sulfones. Thus it was understood that the oral administration was often accompanied by relatively more toxic symptoms due to the more rapid conversion into DDS by the gastric juice[8,38] and that parenteral administration permitted much higher doses[37,39]. Yet nobody appeared to conclude at that time that experiments with very low doses of DDS itself should be the logical consequence. It was only in 1944 that Feldman and colleagues[26] seem to have followed this line of thought in the design of their experiments, but again after fairly positive results they concluded that DDS should be modified.

Work with Promin and other sulfones in tuberculosis was carried on for a while[40,41,42,43], but after 1944 the main interest was concentrated on the antibiotics[27,28,44], as noted above.

Leprosy Treatment with the Proprietary Sulfones

Carville 1941: Promin. It was the preliminary report by Feldman and colleagues of the effect of Promin on experimental tuberculosis, published in 1940[35], which led directly to the use of the sulfones in leprosy[7]. The results of Feldman's group of workers at the Mayo Foundation came to the attention of Dr. Faget, Medical Officer in Charge at the Carville leprosarium in Louisiana, who had long been a student of tuberculosis.

There started in December 1940 an exchange of letters between Dr. Faget and Dr. Sharp, then director of the Department of Clinical Research of Parke, Davis and Co., the producers of Promin. Apart from sending a supply of the drug to Carville, Sharp drew Faget's attention to the study of Promin in rat leprosy, then being conducted by Dr. Cowdry in St. Louis. This initiated a further exchange of letters between Faget and Cowdry. The results in murine leprosy[45] must have encouraged Faget to proceed.

In March 1941 the first administration of Promin to leprosy patients took place. Curiously, although Sharp had emphasized in his letters that the administration of Promin had been limited to the parenteral route, Faget and co-workers decided to give the drug by mouth in a preliminary study[46]. Doses of ½ to 1 g, however, were tolerated for such short periods that therapeutic ef-

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[37] Hinshaw, H. C. and Feldman, W. H. Treatment of experimental tuberculosis. Use of sodium p,p'-diaminodiphenylsulfone-N,N'-didextrose sulfonate ("promin") with notes on some toxic effects observed in man. JAMA **117** (1941) 1066–1068.

[38] Nitti, F., Bovet, D. and Ramon, V. Le sort des aminophénylsulfones dans l'organisme et leur activité antimicrobienne. C. R. Soc. Biol. **138** (1938) 26–28.

[39] Johnson, R. M. Absence of toxic manifestations following the parenteral administration of promin. JAMA **114** (1940) 520.

[40] Hinshaw, H. C., Pfeutze, K. and Feldman, W. H. Treatment of tuberculosis with promin. A progress report. Am. Rev. Tuberc. **47** (1943) 26–34.

[41] Petter, C. K. and Prenzlau, W. S. Treatment of tuberculosis with diasone. Am. Rev. Tuberc. **49** (1944) 308–322.

[42] Petter, C. K. and Prenzlau, W. S. Observation on the clinical application of diasone in human tuberculosis. Ill. Med. J. **85** (1944) 188–197.

[43] Hinshaw, H. C., Feldman, W. H. and Pfeutze, K. H. The clinical administration of 4,2'-diaminophenyl-5'-thiazolesulfone (promizole) in tuberculosis. A preliminary report. Proc. Staff Meet. Mayo Clin. **19** (1944) 33–36.

[44] Feldman, W. H. and Hinshaw, H. C. Effects of streptomycin on experimental tuberculosis in guinea pigs. A preliminary report. Proc. Staff Meet. Mayo Clin. **19** (1944) 593–599.

[45] Cowdry, E. V. and Ruangsiri, C. Influence of promin, starch and heptaldehyde on experimental leprosy in rats. Arch. Pathol. **32** (1941) 632–640.

[46] 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. Public Health Rep. **58** (1943) 1729–1741.

fects seemed unlikely by this method of administration. Severe drug reactions, particularly hemolysis, were so easily provoked that this mode of medication was soon abandoned. Since then intravenous injection has been favored in doses from 1 to 5 g daily for 6 days a week. When some precautions were taken, toxic manifestations were relatively rare and mild.

Oral and pharyngeal lesions were among the earliest to respond to sulfone treatment, and thus the dentist in Faget's group, Prejean, had an opportunity to observe the first beneficial effects of the new drug[47]. The group regarded their work as "the most encouraging experimental treatment ever undertaken at the National Leprosarium." In their conclusions they stated: "While no direct evidence of a specific bacteriostatic or bacteriocidal action against *M. leprae* has been demonstrated, it has been observed that Promin appears capable of inhibiting the progress of leprosy in a considerable percentage of cases. As yet no case of leprosy has become arrested under its influence."

Some years later Faget could report[48], that three years' use of Promin had led to improvement in nearly 100% of the patients—mostly advanced cases—and that 19 patients had been discharged after remaining bacteriologically negative for more than one year.

Diasone and Sulphetrone. When other derivatives of DDS which could be given safely by mouth in similar doses became available, they tended to replace Promin. The most widely used were Diasone and Sulphetrone. They were given in daily doses of 2–6 g[16]. Diasone is the proprietary name for the disodium formaldehydesulfoxylate sulfone, mentioned earlier[22]. The first report of its clinical use in leprosy was made in 1944 by Muir[49], working in Trinidad. Numerous other favorable reports followed and the drug attained wide usage after it was made available commercially in 1946[7]. Sulphetrone is the proprietary name for tetrasodium 4,4′-di(3-phenyl-1,3-disulfopropylamino)-diphenyl sulfone. The first report of its use was made by Wharton in 1947[50]. Sulphetrone proved to be very well tolerated in effective dosage and came into extensive use[7,16]. Two other related sulfones used during this early period of development were Promacetin (or Internal Antiseptic 307)[46] and Promizole[51], but neither of these was used very extensively[16].

Faget[48], comparing Promin, Diasone and Promizole, notes his impression that "the progress of improvement is very similar with each of the three drugs. The diaminodiphenyl sulphone parent radical, common to all, appears to be the active principle." As already mentioned, this was understood by many early workers using sulfones in different types of infections, but like them Faget did not switch over to DDS itself.

Cochrane's dissatisfaction. In 1945 sulfone therapy for leprosy was introduced in Madras under Cochrane's supervision[52]. This leprologist, however, though confirming the effectiveness of the sulfones in leprosy to a large extent, was not really satisfied with the new therapy. In his own words[53]: "In the sulphone drugs we have a new and powerful remedy for advanced lepromatous leprosy, but there is a tendency to treat lightly, or ignore, certain very definite disadvantages in this new therapy. These drawbacks, I believe, are important, and until overcome they will prevent the use of the sulphones for mass treatment such as is necessary in India, Africa or China. The disadvantages are as follows:

1) The method of administration is not suitable for masses of people who are not used to taking large numbers of tablets every day. It is quite impossible to expect success with sulphone therapy by mouth unless the patients are closely supervised.

[47] Prejean, B. M. Chemotherapeutic effect of promin and diasone on oral lesions of leprosy. Dent. Survey **23** (1947) 1411–1416.

[48] Faget, G. H. Chemotherapy of leprosy. Int. J. Lepr. **15** (1947) 7–14.

[49] Muir, E. Preliminary report on diasone in the treatment of leprosy. Int. J. Lepr. **12** (1944) 1–6.

[50] Wharton, L. H. Preliminary report on a new sulphone drug "sulphetrone." Int. J. Lepr. **15** (1947) 231–235.

[51] Faget, G. H., Pogge, R. C. and Johansen, F. A. Promizole treatment of leprosy. A preliminary report. Public Health Rep. **61** (1946) 957–960.

[52] Cochrane, R. G., Ramanujam, K., Paul, H. and Russell, D. Two-and-a-half years' experimental work on the sulphone group of drugs. Lepr. Rev. **20** (1949) 4–64.

[53] Cochrane, R. G. A comparison of sulphone and and hydnocarpus therapy of leprosy. Int. J. Lepr. **16** (1948) 139–144.

2) The cost of these remedies is at present prohibitive and therefore they are out of the question for general use."

It was this dissatisfaction of Cochrane that would lead to a new landmark in leprosy chemotherapy.

Ridley and Jopling[54] define 5 grades of leprosy by reference to the clinical, histological, bacteriological, and immunological patterns: Tuberculoid (TT), Borderline-Tuberculoid (BT), Borderline (BB), Borderline-Lepromatous (BL), and Lepromatous (LL). Leprosy cases not classifiable on this TT-LL scale they call Indeterminate.

The Parent Sulfone DDS in Leprosy

Madras 1946, first DDS injections. Early in 1946, when in Dublin, Cochrane learned that people from the Imperial Chemical Industries (ICI) laboratories at Wilmslow were using the inexpensive parent substance DDS in the treatment of mastitis in cows[55], following the work of McEwen and colleagues mentioned earlier[29]. He got in touch with one of the ICI veterinarians, Dr. Francis, and as a result he took back with him to Madras later that year a suspension of DDS in arachis (peanut) oil. After preliminary trials an experimental treatment group was set up early in 1947.

Reviewing the chemotherapy of leprosy, Bushby[16] states that DDS was not used till 1947. This statement apparently corresponds with Cochrane's own report[56], as described, and with the dates found in case reports mentioned in the extensive review of "Two-and-a-half years' experimental work on the sulphone group of drugs" by Cochrane, Ramanujam, Paul, and Russell[52]. On other occasions, however, Cochrane wrote that "experiments were started in Madras in 1946"[57] and that DDS was "first used at the end of 1946"[58]. These first experiments apparently were the "preliminary trials" referred to[56], after which the experimental treatment group was set up.

The trials[52] were first started on a 15% suspension given intradermally, because it was held by Cochrane that if the bacilli could be prevented from multiplying in the skin, the disease would not progress. When it was found that the substance not only was discovered in the skin of the area which was given intradermal injections but also elsewhere in addition, it was felt that it probably was not worth the pain of the injection, for the same effect could be produced by sub-cutaneous injections.

Massive dose. Cochrane's provisional dose of choice became 5 ml of a 25% suspension of DDS twice a week, giving a total of 2.5 g in the week. Later on, reflecting on these first injections, Cochrane[59] remarks: "It is interesting to note how often success or failure is dependent on a very small margin, for, as this drug had never been used parenterally in man before, so far as is known, the principle of a massive initial dose was adopted and 1.25 g (5 ml) were given twice a week. It was fortunate that the parenteral route was chosen because had this dose been given by mouth disastrous results would have been followed, and a drug which has proved so successful in the therapy of leprosy might have been discarded altogether." It was probably Buttle[56], who had warned Cochrane not to give the drug by mouth because of its toxicity. Cochrane's own belief that parenteral administration of sulfones would reduce the effective dosages[53] rather happily coincided with this warning.

Not for routine treatment. In Madras evidence accumulated that DDS in a 25% suspension of ground nut oil was probably the most potent antileprosy remedy avail-

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[54] Ridley, D. S. and Jopling, W. H. A classification of leprosy for research purposes. Lepr. Rev. **33** (1962) 119–128.

[55] Francis, J. Bacterial chemotherapy in veterinary medicine. Vet. Rec. **59** (1947) 131–137.

[56] Cochrane, R. G. First use of DDS by injection. Recommendations. Int. J. Lepr. **24** (1956) 195–196 (correspondence).

[57] Cochrane, R. G. Chemotherapy in leprosy. Lepr. Rev. **22** (1951) 57–66.

[58] Cochrane, R. G. The administration of diaminodiphenyl sulfone and its derivatives by the oral and parenteral routes, with an assessment of their relative values. Int. J. Lepr. **27** (1959) 68–72 (editorial).

[59] Cochrane, R. G. Therapy. In: *Leprosy in Theory and Practice*. 2nd ed. Cochrane, R. G. and Davey, T. F., eds. Bristol: John Wright & Sons Ltd., 1964, 371–390.

able[52]. This does not mean that the victory of DDS in Madras was complete by 1949. On the one hand toxic signs caused by DDS such as anemia, nausea, and peripheral neuritis were often serious. On the other hand the parenteral administration of Sulphetrone was also very promising, and even the old hydnocarpus medication was still believed to be effective in many cases. This led Cochrane and associates to the advice at the end of their report: "Until a safer dosage of diaminodiphenyl sulphone is worked out we believe that it is reasonable to recommend for the routine treatment of leprosy, particularly for those cases which do not respond to hydnocarpus treatment or which have relapsed, sub-cutaneous injections of 50% sulphetrone in water in a dosage of 7 c.c. twice a week."

At Cochrane's suggestion, Molesworth and Narayanaswami[60], working in Malaya, tried a 20% suspension of DDS in coconut oil in lepromatous leprosy. They reported in 1949 clinical improvement using a dosage of 1 g weekly.

DDS orally, 1948. Quite contrary to Cochrane's ideas, the definite breakthrough in large scale leprosy treatment came by the oral use of DDS, originated in 1948 in three different centers, each center apparently being ignorant of the work of the others.

De Souza Lima[61] in Brazil was the first. His trials commenced in June 1948 in 46 cases of lepromatous leprosy. The dosage was 300 mg daily. Tolerance was good after initial anemia, and the early therapeutic results were promising. Lowe and Smith[6,62] in Nigeria were the second, starting their preliminary trial in October 1948 with nine patients. Beginning with 100 mg daily, they slowly increased the dose and came to a provisional standard daily treatment with 300 mg DDS, based on blood levels and toxicity studies. The third independent start was made by Floch and Destombes[11] in French Guiana. They commenced their trials in November of that same year and had very favorable results with 200 mg DDS daily, be it orally or intramuscularly.

About 14 years later the "priority re oral DDS therapy" would become an argument in the International Journal of Leprosy. While Tréfouël[15] stated that Floch was the first to publish results on this subject, Browne[63] replied that Lowe was the first in treating patients with oral DDS, though not being the first in publication. Browne probably missed the publication of De Souza Lima[61] and its English translation in Leprosy Review[64], for from the date in that paper (11.6.1948) there can be no doubt that De Souza Lima started his trials with oral DDS in leprosy earlier than both Lowe and Floch.

Nigeria. An instructive picture of the introduction of oral DDS administration emerges from the reports about the Nigerian work[6,62,65]. Early in 1947 Dr. Muir, medical secretary of the British Empire Leprosy Relief Association (BELRA), and the biochemist, Smith, had a discussion with Dr. Wevill of ICI. This resulted in a supply of 5 kg of pure DDS for experimental trial by the BELRA Leprosy Research Unit of Nigeria, to be formed later that year under Dr. John Lowe at Uzuakoli.

The Fifth International Leprosy Congress, held in Havana in 1948, recommended a study of DDS injections in small doses. However, Lowe and Smith decided, against all advice, rather to study oral administration in small doses. The oral route was preferred to injection because it was much easier to carry out and, if effective and safe, should prove most economical in drug, staff, labor, and equipment. On a theoretical basis they concluded that the minimum therapeutic blood level of DDS in leprosy might be 10 μg/ml, or even less. The question was whether it was possible in man to

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[60] Molesworth, B. D. and Narayanaswami, P. S. The treatment of lepromatous leprosy with 4:4'-diaminodiphenyl sulfone in oil. Int. J. Lepr. **17** (1949) 197–210.

[61] De Souza Lima, L. Estudos terapeutico-clinico, quimioterapia de lepra. Estudos quimicos, experimentais e terapeutico-clinicos. Rev. Bras. Leprol. **17** (1949) 143–145.

[62] Lowe, J. and Smith, M. The chemotherapy of leprosy in Nigeria. With an appendix on glandular fever and exfoliative dermatitis precipitated by sulfones. Int. J. Lepr. **17** (1949) 181–195.

[63] Browne, S. G. Priority re oral DDS therapy. Int. J. Lepr. **31** (1963) 100 (correspondence).

[64] De Souza Lima, L. Chemotherapy of leprosy. Chemical, experimental and clinical studies. Lepr. Rev. **21** (1950) 36–47.

[65] Smith, M. A pharmacological study of three sulphones. Part III . The specific toxic phenomena. Lepr. Rev. **21** (1950) 17–29.

produce these levels with small oral doses of DDS without toxic effects. Thanks to the excellent absorption of DDS from the gut after oral administration and to its slow elimination, this indeed proved possible with daily doses of 300 mg or even less.

Lowe[6] calculated that the use of oral DDS reduced the cost of sulfone treatment to about a twentieth of the previous figure for Diasone and Sulphetrone treatment. Even treatment with hydnocarpus oil was now no cheaper in Nigeria than with DDS. Lowe concluded that with DDS it should be possible to treat all the thousands of cases of active leprosy in the Nigerian leprosy institutions and that the same would apply in varying degrees for other countries. This indeed was a major breakthrough in the history of leprosy.

Low dosage. It is remarkable that as early as 1937, in the very first paper about the therapeutic value of DDS[5], it is reported that a healthy human individual (G.A.H.B.) had taken 300 mg DDS, which caused no toxic symptoms and gave his blood definite antibacterial properties. Apparently, it took more than ten years before the possible efficacy of this low dose was reconsidered. Curiously, Buttle, the healthy human individual referred to, was one of the researchers who later warned against the extreme toxicity of DDS[56]. We now know, however, of Buttle's early unreported clinical trials with daily doses of 1–2 g DDS, causing serious toxic effects[6,7]. Similar things are known about Feinstone and associates[20,21] and their reports and warnings may likewise have scared other workers. The assumption was made that the dose and concentration attained in the blood had to be of the same order as of the sulfonamides, and such doses proved to be too toxic. There appeared to have been a failure to appreciate the need to compare toxicities of drugs not in terms of weight, but to compare their therapeutic indexes.

It seems that only around 1948 was it fully realized that the proprietary sulfones were both active and toxic through the DDS nucleus[6,11,66], though there had been many early suggestions in that direction[8,37,38,39]. The extremely low quantities of this drug which were active in leprosy must have been unthinkable for the early workers. In this regard one may speculate what the veterinarians would have done and how the course of leprosy history would have run, if 6 rather than 60 μg/ml would have been a well tolerated DDS blood level in cows[29]. There might well have been no history of DDS in leprosy.

In fact the dosage of this drug would remain a major issue in the next thirty years of leprosy history.

THE OPTIMUM DOSE OF DAPSONE IN LEPROSY

Effective Treatment

New hopes. By 1946 the Pan-American Conference on leprosy, held in Rio de Janeiro, gave unqualified support to the sulfones[67]. At the Fifth International Leprosy Congress, held in Havana in 1948, 31 of the 196 papers or titles submitted dealt with this modern treatment, and a great majority accepted the sulfones as drugs of choice in lepromatous leprosy[68]. Although for some years the old chaulmoogra oil remained an important alternative[53,57,67,69], it appeared in 1953 at the Sixth International Leprosy Congress, held in Madrid, that nearly all workers had abandoned its use in favor of sulfone treatment of all forms of leprosy[71].

In the early fifties Sulphetrone was often still considered safer than the parent sulfone[70,72,73,74], but in 1955 Muir could state

[66] Lowe, J. Metabolic fate and determination of sulfones. Int. J. Lepr. **18** (1950) 248–251 (correspondence).

[67] Cochrane, R. G. Sulphone treatment of leprosy. Int. J. Lepr. **17** (1949) 299–304 (editorial).

[68] Wade, H. W. Report on the Havana Congress. Int. J. Lepr **16** (1948) 179–184 (editorial).

[69] Barnes, E. J. and Barnes, J. (Use of DDS abandoned). Lepr. Rev. **22** (1951) 99–100 (correspondence).

[70] Muir, E. Findings of a meeting of leprosy workers. Lepr. Rev. **23** (1952) 30–35.

[71] Gómez Orbaneja, J. (secr.). Treament. Technical resolutions. Sixth International Congress on Leprosy. Int. J. Lepr. **21** (1953) 516–521.

[72] Cochrane, R. G. Report on visit to Nigeria. 15th March to 1 May, 1952. Lepr. Rev. **24** (1953) 33–51.

[73] Cochrane, R. G. Leprosy in Anglo-Egyptian Sudan East and Central Africa. Lepr. Rev. **24** (1953) 177–223.

[74] Davidson, W. S. An evaluation of new treatments and other factors in leprosy. Lepr. Rev. **24** (1953) 139–146.

in an editorial of Leprosy Review[75]: "Now that the rules of its use have been standardised, DDS (whether given orally in tablets or by injection of the suspension) has been accepted almost universally as the treatment of choice." The new hopes raised by the sulfones and especially by DDS were voiced by Floch[76] on the Madrid Congress: "Leprosy is really no longer a 'horrible disease' against which medicine is powerless; it is a disease like any other, that can be foreseen to disappear in practice from the earth's surface in a given period of time, certainly within a man's life time."

Confusion about dosage. Though in Muir's opinion[75] the rules of the use of DDS were standardized by 1955, 14 years later Pearson and Pettit[77] could rightly remark that "no consensus had yet been reached among leprologists concerning the best dosage to be used." In 1973 Naik and co-workers[78] stated: "at present, the fixation of the standard dose in the treatment of leprosy is passing through a confusing phase," and two years later Leiker[79] affirmed that "the optimal dosage scheme of DDS had not yet been established." Only the Fifth Report of the WHO Expert Committee on Leprosy, published in 1977[80], seems to have closed the discussion about the optimum dose of DDS. Many factors in this discussion, lasting nearly 30 years, tended to lower the dosage. One prominent factor, however, gaining weight during the seventies, caused a drastic change in this tendency.

Minimum effective dose. Cochrane and colleagues[52] began their DDS therapy in leprosy with a provisional parenteral dosage of 2.5 g weekly, producing blood levels of 10–30 μg/ml[53]. The three groups initiating oral DDS treatment[6, 11, 61] found dosages of 1.4–2.1 g per week effective, giving blood levels of 5–14 μg/ml[6]. By 1949 Molesworth and Narayanaswami[59] reported that 1 g DDS parenterally per week was as effective as 2.5 g. In the same year Cochrane[67] suggested on a theoretical basis that the effective dosage of DDS might be found to be considerably smaller, possibly as low as 500 mg per week. In 1950 Lowe[81] wrote that 700 mg weekly was usually enough to produce a good clinical and bacteriological response, though he preferred to give more. Floch[76, 82] actually came down to this dosage and even to 500 mg a week in 1953.

In 1950 Muir[83] had observed early clinical signs of improvement in advanced lepromatous cases using DDS dosages as small as 350 mg a week. Two years later Lowe[14] published studies using dosages of 105, 210, 350 and 700 mg per week. He found the speed of response on 350 mg not appreciably slower than in similar cases on the ordinary standard dosage. Even 210 mg a week was capable of producing a clinical response but probably not the maximum response. In 1954 Scohier[84] reported the efficacy threshold for oral DDS treatment of adults to be 300 mg per week. Others went lower, and in 1965 Ramu and Ramanujam[85] found that on 200 mg weekly results were as good as or even slightly better than those obtained on 600 mg weekly. They came to a similar conclusion in a second study, published in 1975[86]. Also Leiker and Carling reported in 1966[87] and again in

[75] Muir, E. Are we satisfied with sulphones for the treatment of leprosy? Lepr. Rev. **26** (1955) 135–136 (editorial).

[76] Floch, H. La thérapeutique antilépreuse actuelle. Arch. Inst. Pasteur Guyane Fr. et de l'Inini Publ. No. 303, Novembre 1953.

[77] Pearson, J. M. H. and Pettit, J. H. S. Chemotherapeutic trials in leprosy. 7. Trial of 50 mgm DDS twice weekly in the treatment of lepromatous leprosy. Int. J. Lepr. **37** (1969) 40–45.

[78] Naik, S. S., Sane, A. B. and Ganapati, R. Absorption and excretion of dapsone in leprosy patients. Indian J. Dermatol. Venereol. **39** (1973) 68–78.

[79] Leiker, D. L. Chemotherapy in leprosy. Int. J. Dermatol. **14** (1975) 254–262.

[80] World Health Organization. WHO Expert Committee on Leprosy Fifth Report. WHO Tech. Rep. Ser. No. 607, 1977.

[81] Lowe, J. Dosage of diamino-diphenyl-sulphone. Lancet **2** (1950) 36–37.

[82] Floch, H. and Gélard, A. Il est possible en thérapeutique antilépreuse de ne pratiquer qu'une injection intramusculaire toutes les trois semaines de 1 gr 50 de D.D.S. en eau gélosée. Arch. Inst. Pasteur Guyane Fr. et de l'Inini Publ. No. 312, Décembre 1953.

[83] Muir, E. Preliminary report on 4:4′ diaminodiphenyl sulfone (DDS) treatment of leprosy. Int. J. Lepr. **18** (1950) 299–308.

[84] Scohier, L. La posologie des sulfones en thérapeutique de masse. Ann. Soc. Belge Méd. Trop. **34** (1954) 637.

[85] Ramu, G. and Ramanujam, K. Lower dosage sulphone regimen in leprosy. Lepr. India **37** (1965) (Suppl. 3A) 293–299.

[86] Ramanujam, K., Iyer, C. G. S. and Ramu, G. A report on a controlled clinical trial with conventional and one third conventional dose of dapsone administered orally once a week in lepromatous patients. Lepr. Rev. **46** (1975) (Suppl.) 93–97.

[87] Leiker, D. L. and Carling, D. Low dosage of DDS. Lepr. Rev. **37** (1966) 27–29.

1969[88] that 200 mg DDS per week was effective in uncomplicated lepromatous leprosy. Meanwhile Browne[89], Pettit and Rees[90], and Pearson and Pettit[77] studied the response of lepromatous leprosy on 100 mg DDS per week. They all found it fully effective in this dosage.

Jopling[91], however, would not consider such doses meriting the descriptions "low DDS dosage." Already in 1965[92] he commented in a discussion about leprosy reactions, that "anyone who tries giving 5 mg twice a week . . . will be pleasurably surprised at the steady improvement in smears and biopsies." In the same year Cochrane[93] reported clinical improvement in three patients that had been given not more than 30 mg DDS a week—one was actually taking 20 mg. And indeed, following the discovery of Shepard and colleagues[94] in 1966 that the minimal inhibitory concentration (MIC) of DDS for the growth of *M. leprae* in mice was in the order of a few nanograms per ml of blood, Waters and co-workers undertook a pilot trial giving 1 mg DDS per day to 7 previously untreated patients suffering from lepromatous leprosy. In 1968[95] they reported at the Ninth International Leprosy Congress, held in London, that after 4.5 months clinical and bacteriological results were encouraging, and in 1971[96] they wrote that the completed clinical trial had established the effectiveness of that dosage of DDS.

In 1969, however, Karat and co-workers[97] published a less optimistic paper about low DDS doses, showing that 30–60 mg per week was not effective in lepromatous leprosy. Two years later the tide appears to have changed, when Prasad[98] advocated 1200 mg DDS per week in the treatment of tuberculoid leprosy, showing the superior efficacy and secondary advantages of this high dosage. Nevertheless, studies[99, 100] continue to show that the MIC of DDS for *M. leprae* is only a few nanograms per ml, but for reasons to be discussed later the old advocates of low dosages have become silent.

Mode of action. It is interesting to see how ideas about the mode of action of DDS influenced, e.g., Cochrane in his search for the optimum dosage. In 1949[101] he commented on his initial doses: "We have always gone on the principle that as diaminodiphenyl sulphone is a chemotherapeutic agent, as high a dose as possible should be given." The chemotherapeutic action was understood as antagonism of p-aminobenzoic acid (PABA) in folic acid biosynthesis[102, 103, 104, 105]. Throughout the years most

[88] Leiker, D. L. and Carling, D. Second trial of low dosage of DDS in lepromatous leprosy. Lepr. Rev. **40** (1969) 54–58.

[89] Browne, S. G. Low-dose oral dapsone. Interim report. Lepr. India **37** (1965) (Suppl. 3A) 299–302.

[90] Pettit, J. H. S. and Rees, R. J. W. Chemotherapeutic trials in leprosy. 4. Dapsone (DDS) in low dosage in the treatment of lepromatous leprosy. A demonstration pilot study. Int. J. Lepr. **35** (1967) 140–148.

[91] Jopling, W. H. Low doses of dapsone in the treatment of leprosy. Int. J. Lepr. **40** (1972) 419 (correspondence).

[92] Jopling, W. H. (Dr. Sheskin's paper). Lepr. Rev. **37** (1965) 186–187 (comments).

[93] Cochrane, R. G. The need for bringing leprosy research into universities. Int. J. Lepr. **33** (1965) 403–411.

[94] Shepard, C. C., McRae, D. H. and Habas, J. A. Sensitivity of *Mycobacterium leprae* to low levels of 4,4′-diaminodiphenyl sulfone. Proc. Soc. Exp. Biol. Med. **122** (1966) 893–896.

[95] Waters, M. F. R., Rees, R. J. W. and Ellard, G. A. Experimental and clinical studies on the minimum inhibitory concentration (MIC) of dapsone (DDS) in leprosy. Int. J. Lepr. **36** (1968) 651.

[96] Ellard, G. A., Gammon, P. T., Rees, R. J. W. and Waters, M. F. R. Studies on the determination of the minimum inhibitory concentration of 4,4′-diaminodiphenyl-sulphone (dapsone, DDS) against *Mycobacterium leprae*. Lepr. Rev. **42** (1971) 101–117.

[97] Karat, A. B. A., Jeevaratnam, A. and Rao, P. S. S. An open trial of low doses of dapsone in the management of lepromatous leprosy. Lepr. Rev. **40** (1969) 99–105.

[98] Prasad, B. N. Trial of high dosages of dapsone in the treatment of tuberculoid leprosy. Lepr. Rev. **42** (1971) 118–120.

[99] Peters, J. H., Gordon, G. R., Murray, J. F., Fieldsteel, A. H. and Levy, L. Minimal inhibitory concentration of dapsone for *Mycobacterium leprae* in rats. Antimicrob. Agents Chemother. **8** (1975) 551–557.

[100] Levy, L. and Peters, J. H. Susceptibility of *Mycobacterium leprae* to dapsone as a determinant of patient response to acedapsone. Antimicrob. Agents Chemother. **9** (1976) 102–112.

[101] Cochrane, R. G. (cited in editorial). Lepr. Rev. **20** (1949) 3.

[102] Steenken, W. and Heise, P. H. Action of promin and diamino-diphenyl sulfone upon tubercle bacilli. Antipromin action of p-amino-benzoic acid. Proc. Soc. Exp. Biol. Med. **52** (1943) 180–183.

[103] Brownlee, G., Green, A. F. and Woodbine, M. Sulphetrone: a chemotherapeutic agent for tuberculosis. Pharmacology and chemotherapy. Br. J. Pharmacol. **3** (1948) 15–28.

[104] Donovick, R., Bayan, A. and Hamre, D. The reversal of the activity of antituberculous compounds *in vitro*. Am. Rev. Tuberc. **66** (1952) 219–227.

[105] Browne, G. M. Inhibition by sulfonamides of the

authors[106, 107, 108, 109, 110, 111, 112] have considered this at least as one important part of the essentially bacteriostatic action of DDS on micro-organisms.

In 1950, however, Rath de Souza and De Souza Lima[113] drew attention to the degeneration of the histiocytic (Virchow) cells, caused by DDS. This process appeared to begin before the disintegration of *M. leprae* present in these cells. Their hypothesis therefore was that the sulfones act principally on the Virchow cell, in some way altering its metabolism and making its cytoplasm unsuitable for the life of *M. leprae*. In 1956[114] and repeatedly thereafter[115, 116, 117] Bergel interpreted the mechanism of action of the sulfones against leprosy on the basis of an antioxidant activity, protecting the lipoproteic membrane of lysosomes and thus increasing the defensive capacity of the organism.

It is this idea about lysosomes that changed the policy of Cochrane. In 1965[93] he relates how he was instructed by Dr. Brieger about the function of these organelles, and how shortly thereafter Dr. Fell explained to him that "certain drugs in small doses activate lysosomes and in large doses inhibit lysosomal action." Cochrane therefore suggested that "when a case relapses it is not a true relapse, but that the continuous administration of large doses of DDS so inhibits lysosomal activity that it enables the *Mycobacterium leprae* to multiply within the macrophage cells. When the dose is reduced to almost a homeopathic level, the drugs begin to act in the opposite way and activate lysosomal action and enable the enzymes, presumably of a lysosomal nature, to destroy the bacilli."

The concept that DDS may be acting on, or through, lysosomal enzymes was further investigated by Prabhakaran and Bapat in 1966[118] and by Palekar and Magar in 1967[119]. A few years later Morrison[109] hypothesized that "DDS interaction with lysosomal membranes results in permeability changes and the subsequent concentration of DDS within the organelle . . . . Thus through discharge of lysosomal contents into the phagosome a localized concentration gradient of DDS is available to exert antifolate effects upon phagocyted mycobacteria." Tsutsumi and co-workers explained in 1977[120] some experimental results in terms of a "tidal wave action of DDS," first stabilizing lysosomal membranes, and in a later stage accelerating the NAD-NADH system inside the macrophage.

Also today the specifically low MIC of DDS for *M. leprae* continues to puzzle the

biosynthesis of folic acid. Int. J. Lepr. **35** (1967) 530–589.

[106] Naylor, R. F. A study of the action of sulfones on the metabolism of mycobacteria. Int. J. Lepr. **26** (1958) 313–317.

[107] Naylor, R. F. and Hanks, J. H. The influence of 4,4′-diaminodiphenyl sulfone (DDS) on the respiration, reproduction and mutation of mycobacteria. Int. J. Lepr. **29** (1961) 56–64.

[108] Pattyn, S. R. and Van Ermengem, J. DDS sensitivity of mycobacteria. Antagonistic effect of PABA for *M. ulcerans* and *M. kansasii*. Int. J. Lepr. **36** (1968) 427–431.

[109] Morrison, N. E. Sequential blockade of the mycobacterial *de novo* folate pathway. A review. Int. J. Lepr. **39** (1971) 34–43.

[110] Colwell, W. T., Brown, V. H., De Graw, J. I. and Morrison, N. E. Studies on the mechanism of action of dapsone. Int. J. Lepr. **41** (1973) 484.

[111] Panitch, M. L. and Levy, L. The action of dapsone on a susceptible strain of *Mycobacterium kansasii*. Lepr. Rev. **49** (1978) 131–140.

[112] Seydel, J. K., Richter, M. and Wempe, E. Mechanism of action of the folate blocker diaminodiphenylsulfone (dapsone, DDS) studied in *E. coli* cell-free enzyme extracts in comparison to sulfonamides (SA). Int. J. Lepr. **48** (1980) 18–29.

[113] Rath de Souza, P. and de Souza Lima, M. The mechanism of action of the sulfone derivatives in lepromatous leprosy. Int. J. Lepr. **20** (1952) 365–374.

[114] Bergel, M. Mecanismo de la actividad antileprótica de las sulfonas. Leprología **1** (1956) 156–166.

[115] Bergel, M. Consideraciones sobre quimioterapia de la lepra. Leprología **2** (1957) 107–110.

[116] Bergel, M. Lysosomes. Their relationship with vitamin E and leprosy. Lepr. Rev. **38** (1967) 189–192.

[117] Bergel, M. Actividad cancerigena de la diaminodifenilsulfona (D.D.S.). Pub. Est. Leprol. **13** (1973) 30–41.

[118] Prabhakaran, K. and Bapat, C. V. Effect of diaminodiphenyl sulfone and ICRC bacilli on acid phosphatase of macrophages. Indian J. Med. Res. **54** (1966) 458–461.

[119] Palekar, A. G. and Magar, N. G. Effects of DDS on lysosomal enzymes from leprosy tissues. Int. J. Lepr. **35** (1967) 436–445.

[120] Tsutsumi, S., Gidoh, S., Narita, M., Koide, S. and Funazu, T. The characteristic anti-inflammatory effects of several anti-leprosy drugs. Int. J. Lepr. **46** (1978) 113–115.

researchers, inducing them to consider alternative modes of action. Recently Panitch and Levy[111] showed that *M. kansasii* accumulates DDS against a concentration gradient, suggesting a basis for the prolonged bacteriostatic action of DDS. The activity was quantitatively antagonized by PABA, but "the 100-fold greater MIC for *M. kansasii* than for *M. leprae* suggests that the actions of the drug on the 2 organisms may differ qualitatively as well as quantitatively." Extensive biochemical studies by Seydel and co-workers[112] support this idea. They outline several hypotheses, two of which are of particular interest. The first is the powerful effect of the inhibition of folate metabolism by DDS that would occur if folate metabolism is the rate determining step for the extremely slow generation rate of *M. leprae*. The second is the possible inhibitory effect of DDS, also at a second stage in the pathway of folic acid biosynthesis.

Perhaps the most recent hypothesis for the mechanism of action of DDS against *M. leprae* comes from Prabhakaran and colleagues[121]. They found that DDS inhibits orthodiphenoloxidase, "the only enzyme proven to be present in the leprosy organisms." They suppose that the sulfur atoms of DDS bind the copper of the enzyme and thus inactivate it, if only the drug is able to penetrate the bacterium.

Untoward Effects

Toxic effects. In Graham's[122] words "haematologic toxicity (especially haemolytic anaemia and methaemoglobinaemia) is the hallmark of dapsone toxicity." The nearly ten years' delay in clinical work with DDS was apparently caused by the hemolytic crises following the clinical trials in 1937 and 1938 with doses of 1–2 g a day[6,7,21]. When DDS was finally introduced in leprosy, it was soon found that the anemia caused by 200–300 mg a day was of a mild self-correcting type[61,123]. According to Smith[65] the maximum tolerated dose was 500 mg daily, at which a marked hemolytic process commenced. Brownlee[124] recorded no acute crisis with a DDS blood level under 30 μg/ml. In 1952 Lowe[14] put this threshold at 20 μg/ml. He reported that a level of 10–20 μg/ml was free of acute toxicity but led to chronic toxicity, whereas 2–10 μg/ml was really safe. Nahas and colleagues[125] found in 1954 that blood concentrations of DDS over 6 μg/ml induced a moderate, progressive anemia. Blood concentrations smaller than that amount did not cause any alterations.

Psychosis is another toxic effect that fostered the reduction of DDS dosages. At doses of 200–300 mg a day this complication was not uncommon[14,126,127,128,129], but in 1951 a meeting of leprosy workers convened by the British Empire Leprosy Relief Association (BELRA) noted that at lower doses phychosis is rare[70]. This is confirmed by Graham[122] in his extensive review of the adverse effects of dapsone, published in 1975.

Dermatitis is considered by Cochrane[59] as "probably the most serious and certainly one of the most distressing of the complications of sulphone therapy." Lowe mentioned in some of his publications[62,127] this complication in a frequency of 2% of his patients while Garrett noticed a frequency of 2–3% among his patients[128,129,130]. If this drug fever ensues there is a grave danger of an exfoliation developing, and along with this, hepatitis. This condition has not infre-

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[121] Prabhakaran, K., Harris, E. B. and Kirchheimer, W. F. A possible method for improving the efficacy of dapsone (personal communication).

[122] Graham, W. R. Adverse effects of dapsone. Int. J. Dermatol. **14** (1975) 494–500.

[123] Smith, M. A pharmacological study of three sulphones. Part II. Hydrolysis and the specific toxic phenomena. Lepr. Rev. **20** (1949) 128–134.

[124] Brownlee, G. (Early experiences with DDS in man). Int. J. Lepr. **18** (1950) 247–248 (correspondence).

[125] Nahas, L., Rzeppa, H. and De Souza Lima, L. Blood picture in sulfone treatment of leprosy. Relation with the dose and blood concentration of the drugs. Int. J. Lepr. **22** (1954) 22–30.

[126] Lowe, J. Sundry experiences in the chemotherapy of leprosy. Int. J. Lepr. **19** (1951) 15–21.

[127] Lowe, J. Diaminodiphenylsulphone in the treatment of leprosy. Lancet **1** (1951) 18–21.

[128] Garrett, A. S. Mass treatment of leprosy with D.A.D.P.S. (Dapsone). Lepr. Rev. **22** (1951) 47–53.

[129] Garrett, A. S. and Corcos, M. G. Dapsone treatment of leprosy. Lepr. Rev. **23** (1952) 106–108.

[130] Garrett, A. S. Five years of mass dapsone (DDS) treatment. Lepr. Rev. **26** (1955) 54–60.

quently been fatal. For Barnes and Barnes in the early fifties this was first a reason to reduce their daily doses of 200 mg and see whether doses varying from 50 to 130 mg daily would be effective and non-toxic[131], and then a reason to completely abandon the use of DDS[69]. Lowe, however, wrote in 1952[14] that "this danger can be greatly reduced by a slow induction of treatment, the standard dose not being attained for several weeks."

Sulfone therapy is associated also with agranulocytosis. In 1949 Lowe and Smith[62] described in leprosy patients a clinical picture resembling infectious mononucleosis. They considered this to be true infectious mononucleosis precipitated by sulfone therapy. In 1950 Sloan and colleagues[132] mentioned a leprosy patient dying of agranulocytosis, possibly related to sulfone treatment. Leiker reported in 1956[133] agranulocytosis in 3 DDS treated leprosy patients with a "mononucleosis syndrome." Since then agranulocytosis also has been described in cases where DDS was used for treatment of dermatitis herpetiformis[134], psoriasis[135], and acne vulgaris[136], and where DDS was used for malaria prophylaxis[137].

Other toxic effects of DDS are rare and do not appear to have influenced the dosage schemes in leprosy. Graham[122] concludes his review with the following words: "In the reports of early workers who saw most of the toxic effects of dapsone there is a fairly common theme: toxicity is seen early in the course of high dose administration. The lesson is self-evident."

Lepra reactions. In the words of the Fifth Report of the WHO Expert Committee on Leprosy, published in 1977[80]: "Most reactions seen in leprosy control schemes belong to one of two main types, namely, erythema nodosum leprosum (lepromatous lepra reaction) and reversal reaction. The former occurs in lepromatous (LL) and small numbers of borderline (BL) patients; the latter is related to an increase in specific cell-mediated immunity and occurs in borderline (BT, BB and BL) leprosy usually soon after chemotherapy has been started. Reactions in TT leprosy are probably akin to reversal reaction." The dosage schemes of DDS in leprosy have been greatly influenced by the incidence and severity of these reactions. In the following historical account the reservation must be made that not all leprologists have always used the same terms for the same phenomena.

In retrospect it is as if the Fifth International Leprosy Congress, held in Havana in 1948, wanted to set the scene for thirty years, and maybe more, of discussion about this theme. In the words of its Committee on Therapy, speaking about reactions such as erythema nodosum leprosum (ENL) appearing or exacerbating at some stage of sulfone therapy, "these phenomena may indicate an increase or decrease of dosage or a temporary suspension of the treatment[68]."

The ambivalent character of this advice is reflected in many following remarks of Cochrane, who was the committee's secretary. An anthology: "All patients on sulphone therapy, especially with diasone, should be warned that a period of reaction is to be expected during the first 6 months of treatment. Because reaction tends to subside on continuation of treatment, and is less marked when maximum dosages are reached, I believe that the dose should be increased rapidly, and that frequent rest periods are not necessary. We have therefore adopted the policy of reaching maximum dosages in the shortest possible time." And: "lepra reaction, particularly of the erythema nodosum type, is generally seen at the lower dose levels[138]." Shortly after that: "The whole question of dosages and

[131] Barnes, J. and Barnes, E. J. Liver damage during treatment with diaminodiphehylsulfone. Lepr. Rev. **22** (1951) 54–56.

[132] Sloan, N. R., Chung-Hoon, E. K., Godfrey-Horan, M. E. and Hedgcock, G. H. Sulphone therapy in leprosy. A three year study. Int. J. Lepr. **18** (1950) 1–9.

[133] Leiker, D. L. The mononucleosis syndrome in leprosy patients treated with sulfones. Int. J. Lepr. **24** (1956) 402–405.

[134] McKenna, W. B. and Chalmers, A. C. Agranulocytosis following dapsone therapy. Br. Med. J. **1** (1958) 324–325.

[135] Levine, P. H. and Weintraub, L. R. Pseudoleukemia during recovery from dapsone-induced agranulocytosis. Ann. Int. Med. **68** (1968) 1060–1065.

[136] Firkin, F. C. and Mariani, A. F. Agranulocytosis due to dapsone. Med. J. Aust. **2** (1977) 247–251.

[137] Ognibene, A. J. Agranulocytosis due to dapsone. Ann. Int. Med. **72** (1970) 521–524.

[138] Cochrane, R. G. New developments in the therapy of leprosy. Int. J. Lepr. **17** (1949) 283–293.

reaction needs to be carefully worked out . . . . It may be that smaller dosages are more effective in tiding over the reaction period[52]." And again in the same year (1949): "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[67]." According to data published by Muir in 1951[139], reaction indeed appeared to be beneficial in causing elimination of bacilli, and he raised the question of the desirability of promoting their absorption by deliberately inducing reaction.

Floch and Destombes[140] noticed in 1950 that the frequency of lepra reactions was much lower after parenteral administration (8%) than after oral administration of DDS (47%). The same was noticed in the French African Federations by Giaquinto and Gilbert[141, 142]. In the early fifties promotors of the oral DDS treatment largely adopted twice weekly instead of daily doses. According to Ramanujam and Ramu[143] there was "no disagreement regarding the frequency of administration since at that time all of us were so much used to twice a week regimen of treatment with hydnocarpus oil." Garrett[128, 129] informs us that the twice weekly dosages greatly reduced both the frequency and the severity of the reactions. However, using a suspension of DDS in oil, Roy[144] found 63.5% of his patients suffering from lepra reactions even on bi-weekly injections of as little as 200 mg DDS.

In 1955 Garrett[130] warned about tuberculoid nerve reactions, which might be avoided by starting treatment on a low dosage for those at risk, with a maximum of 200 mg twice weekly for at least three months. Lewis and colleagues[145] did not agree with Garrett. Following 122 cases of the tuberculoid type for an average of six months, they found that DDS treatment with 100 mg a day right from the start did not cause more or worse reactions. One of this group of workers had observed something similar with ENL among lepromatous cases. In 1961 Doull and co-workers[146] reported reactions to be equally frequent whether a lepromatous patient of 60 kg received 150 mg or 240 mg DDS daily. The Eighth International Leprosy Congress, held in 1963 in Rio de Janeiro, advised through its Panel on Lepra Reactions[147] that "specific treatment of leprosy should be maintained, lessened or stopped altogether, according to the severity of the reactional state."

A few years later Davey[148] warned that 100 mg DDS a day risks inducing reactive phases, and, contributing to the same discussion, Jopling[91] remarked that he "would consider it unwise to give as much as 100 mg in one month" to patients who are reacting, "let alone in one day." Also Trautman[149] suggested in this year (1965), that in severe cases of ENL sulfone dosage should be discontinued, and Ramu and Ramanujam[85] found that lepra reaction had a definitely lower incidence in patients receiving smaller doses of DDS, such as 200 mg a week. Browne[89] confirmed this, and Chat-

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[139] Muir, E. Bacteriological changes under DDS treatment of leprosy. Lepr. India **23** (1951) 116–126.

[140] Floch, H. and Destombes, P. Rôle de la thérapeutique sulfonée sur l'apparition et l'évolution des réactions lépreuses: reactions léprotiques et tuberculoïdes réactionelles. Arch. Inst. Pasteur Guyane Fr. et de l'Inini Publ. No. 218, Octobre 1950.

[141] Giaquinto, M. Mass treatment with DDS by injection in the French African Federations. Int. J. Lepr. **24** (1956) 216–218.

[142] Giaquinto, M. and Gilbert, M. The use of parenteral administration of "repository drugs" in individual therapy and in mass treatment campaigns. Acta Leprol. **12** (1963) 3–25.

[143] Ramanujam, K. and Ramu, G. Two decades of sulphone therapy in leprosy. Lepr. India **40** (1968) 106–110.

[144] Roy, A. T. Suspension of diaminodiphenylsulphone in leprosy. Lepr. Rev. **23** (1952) 73–79.

[145] Lewis, R. A., Kyi-Kyi, K. and Edwards, R. Initial dosage of diaminodiphenylsulfone in the treatment of tuberculoid leprosy. Int. J. Lepr. **25** (1957) 370–374.

[146] Doull, J. A., Rodriguez, J. N., Tolentino, J. G., Fernandez, J. V., Guinto, R. S., Rivera, J. N. and Mabaley, M. C. Clinical evaluation studies in lepromatous leprosy fourth series: 4,butoxy-4'dimethylaminodiphenyl thiourea (DPT), amodiaquin, and 4-4'diaminodiphenyl sulfone (DDS) 2.5 mgm and 4 mgm per kg of body weight. Int. J. Lepr. **29** (1961) 291–317.

[147] Ridley, D. S. (secr.). Report of the panel on lepra reaction. Report on the Rio de Janeiro Congress. Int. J. Lepr. **31** (1963) 480–482.

[148] Davey, T. F. (Dr. Sheskin's paper). Lepr. Rev. **36** (1965) 186 (comments).

[149] Trautman, J. R. The management of leprosy and its complications. N. Engl. J. Med. **273** (1965) 756–758.

terjee[150] had the experience that after an initial dose of 25 mg of DDS symptoms of reaction developed, while later after 5 mg per day and a gradual increase of the dose no reaction occurred.

In 1967 however, Pettit and Waters[151] showed in a study of 60 cases that it is not the DDS that causes the ENL and thus it would be illogical to stop DDS during reactions as suggested, e.g., by the Third Report of the WHO Expert Committee on Leprosy, published in 1966[152]. Yet Ramanujam and Ramu[143] maintained that in reaction even the smallest dose of DDS of the order of 1 mg is not tolerated even while the patient is on steroids. Karat and co-workers[97] had indications that the severity of ENL may be dose-related, while the incidence of ENL may be unrelated to dosage. Leiker and Carling[87,88] found no relation between dosage and the frequency or severity of ENL, nor did Pearson and Pettit[77]. In 1973 Helmy and co-workers[153] reported to the Tenth International Leprosy Congress, held in Bergen, that a start with 100 mg DDS daily had no effect on the ENL and that 100 mg DDS daily given to patients suffering from proven sulfone-resistant lepromatous leprosy and receiving effective alternative treatment did not precipitate ENL or increase its severity. This showed that DDS is at least no direct cause of ENL. At the same Congress Merklen and colleagues[154] presented a paper saying that starting treatment with 150 mg DDS a day, followed by a maintenance dose of 100 mg a day, does not cause an increase in the frequency of reactional episodes.

A year later, Browne[155] warned again of the danger of severe peripheral nerve damage in tuberculoid or near-tuberculoid leprosy, if DDS is given in too high a dose at the beginning of treatment, but in 1976 Barnetson and co-workers[156] showed that the incidence of this type of reaction is at least as high on 5 mg as on 50 mg DDS per day. They found that DDS in the higher dosage has an immunosuppressive effect and therefore diminishes the risk of a disabling reversal reaction. Recent studies seem to confirm this immunosuppressive activity of DDS[120,157,158].

Yet, conflicting reports still appear. Thus in the Workshop on Leprosy Control in Asia, held in 1977, Dr. Lopez-Bravo[157] told about his experience in altering the dosage scheme from 100 mg or 200 mg DDS a week to 100 mg daily: "The increase of lepra reaction, specifically in the borderline lepromatous reversal reaction, is fantastic and now the hospital is full." But in the same Workshop Dr. Kosasih[160] reported a therapeutic trial that he called a "bulldozer approach." Lepromatous patients received daily simultaneously 600 mg rifampin, 200–300 mg DDS, 200–300 mg INH and 250–375 mg prothionamide. The report says: "The leprosy reaction of the ENL type which occurred during this treatment was still there, although at a minor stage which did not need additional treatment." Also in recent studies in India it was concluded that because of the neurotoxic effect, relatively high doses of DDS might enhance the risk

[150] Chatterjee, A. Clinical evaluation of the dosage of DDS. Indian J. Dermatol. **11** (1966) 158–159.

[151] Pettit, J. H. S. and Waters, M. F. R. The etiology of erythema nodosum leprosum. Int. J. Lepr. **35** (1967) 1–10.

[152] World Health Organization. WHO Expert Committee on Leprosy Third Report. WHO Tech. Rep. Ser. No. 319, 1966.

[153] Helmy, H. S., Pearson, J. M. H. and Waters, M. F. R. Relation of dapsone (DDS) therapy to erythema nodosum leprosum. Is it direct or indirect? Int. J. Lepr. **41** (1973) 692.

[154] Merklen, F. P., Cottenot, F. and Pennec, J. More rapid bacterial negativation and clinical clearing in leprosy by increasing the doses of anti-leprosy drugs. Int. J. Lepr. **41** (1973) 692.

[155] Browne, S. G. Drug resistance in leprosy. Lepr. Rev. **45** (1974) 276–278.

[156] Barnetson, R. StC., Pearson, J. M. H. and Rees, R. J. W. Evidence for prevention of borderline leprosy reactions by dapsone. Lancet **2** (1976) 1171–1172.

[157] Stendahl, O., Molin, L. and Dahlgren, C. The inhibition of polymorphonuclear leukocyte cytotoxicity by dapsone. A possible mechanism in the treatment of dermatitis herpetiformis. J. Clin. Invest. **62** (1978) 214–220.

[158] Sengupta, U., Ghei, S. K., Venkatesan, K. and Bharadwaj, V. P. *In vivo* effect of DDS on phytohemagglutinin (PHA)-induced lymphocyte transformation cultures in normal healthy volunteers. Int. J. Lepr. **47** (1979) 167–170.

[159] Lopez-Bravo, L. (Chemotherapy). In: *Proceedings of the 1st International Workshop on Leprosy Control in Asia*. Tokyo: Sasakawa Memorial Health Foundation, 1977, p. 143 (discussion).

[160] Kosasih, A. Integrated treatment of leprosy at Dr. Cipto Mangunkusumo General and Teaching Hospital, Jakarta. In: *Proceedings of the 1st International Workshop on Leprosy Control in Asia*. Tokyo: Sasakawa Memorial Health Foundation, 1977, 43–60.

of deformities[161], but ENL was not related to DDS therapy[162].

Clearly the last word about DDS and lepra reactions has not really been said, for there are still enough researchers who would not agree with what Taylor and coworkers wrote in 1976[163]: "The association with reactive episodes is significant only in that it has affected the dose and regularity of prescription."

Supervision difficult. In 1948 Lowe[164] complained that countries such as West Africa were obtaining hydnocarpus oil from India "often of miserably poor quality, and at no cheap price," but also the proprietary sulfones, though effective, were dear. The drug of choice for mass treatment of leprosy had first of all to be cheap, and secondly it should be easy to administer[52, 67, 165]. In this regard Smith said in 1949[166] that the most desirable sulfone is one by which blood and tissue levels of a therapeutic order may be maintained on "small, widely spaced doses, thus reducing the cost of therapy, and making possible mass oral treatment with the minimum of staff." Apparently DDS was this most economical and convenient sulfone[6, 62, 71, 126].

Caution to avoid toxic effects and reactions induced leprosy officers to lower the dosage where supervision was difficult. In his report on a visit to Nigeria Cochrane[72] says: "If it had not been for the modification of DDS therapy by lowering the dosage, and giving the tablets twice a week instead of daily, it would have been difficult to continue oral DDS as an out-patient treatment." In India, Gilbert[167] gave 700 mg a week to patients who could only attend the clinic at monthly intervals but to "less intelligent patients" he would give only half of this, and those patients who came for weekly DDS injections but failed to attend regularly, were punished by reduction in dose or suspension of treatment. The official advice of the Leprosy Advisory Committee of India was to give to out-patients maximally ⅔ of the dose given to in-patients[143]. In a recent editorial in the International Journal of Leprosy, Lechat[168] describes the situation as follows: "Convenience was the leitmotiv. From a fortunate logistic context it tended to transform into a myth to which leprosy had to adhere. Since very high dosages administered at the beginning of the sulfone era were in all likelihood associated in leprosy patients with a high incidence of lepra reaction and other complications such as dermatitis and psychosis, lower doses were recommended, which relaxed the requirements for medical supervision and lifted the possible need for facilities to hospitalize reactional patients."

Sulfone Resistance

No indication. Reflecting on the Pan American Leprosy Conference, held the year before in Rio de Janeiro, Floch wrote in 1947[169]: "Finally, one question that seems interesting to us has not been considered, namely that of possible drug resistance of the Hansen Bacillus towards the sulfone compounds." Two years later, Floch and Destombes[11] said they did not expect this danger from the short rest period advised in sulfone treatment. Also Lowe[164] and Cochrane[67] warned in these early years that sulfone resistance could not be excluded, and Garrett expressed as early as 1951[128] his fear that in Nigeria a flourishing black market might lead to drug resistant strains within a few years.

The BELRA meeting of leprosy workers,

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[161] Gupte, M. D. Dapsone treatment and deformities. A retrospective study. Lepr. India **51** (1979) 218–235.

[162] Dutta, R. K. A study of patients with erythema nodosum leprosum syndrome. Lepr. India **51** (1979) 209–212.

[163] Taylor, P. M., Chacko, C. J. G. and Job, C. K. Study of sulphone resistance in leprosy patients in India. Lepr. Rev. **47** (1976) 5–11.

[164] Lowe, J. Sulphone treatment of leprosy. Lepr. Rev. **19** (1948) 129–138.

[165] World Health Organization. Inter-regional leprosy conference. Tokyo, 20–24 November 1958.

[166] Smith, M. A pharmacological study of three sulphones. Part I. Absorption, distribution and excretion. Lepr. Rev. **20** (1949) 78–88.

[167] Gilbert, D. J. Notes on a year of treatment of out-patients with diamino-diphenyl-sulphone with special mention of the treatment of eye-complications in out-patients. Lepr. India **25** (1953) 29–31.

[168] Lechat, M. F. Sulfone resistance and leprosy control. Int. J. Lepr. **46** (1978) 65–67 (editorial).

[169] Floch, H. Huile de chaulmoogra et médicaments sulfonés dans le traitement de la lèpre. Arch. Inst. Pasteur Guyane Fr. et de l'Inini Publ. No. 159, Août 1947.

held in 1951[170], states that "so far no clear indication of any kind has been seen to show that prolonged or intermittent sulphone treatment produces sulphone resistant bacilli in the person treated." The Committee on Therapy of the Sixth International Leprosy Congress, held in Madrid in 1953[170], came to a similar conclusion. Floch[76] however, warned the Congress about the danger of low dosages: "It is by using unthoughtfully low therapeutic doses, that one risks inducing 'sulphone resistance' of the Hansen Bacillus. Until now, it is said, one has not observed it; that is very fortunate, but once discovered, it will be a bit too late!" But in the late fifties Chaussinand and Bourcart[171] found this fear of small doses to have "no foundation, since from 1948 no characteristic case of resistance to sulphones can be found among the hundreds of thousands of patients who undergo, more or less regularly, treatment by DDS." Actually, the absence of resistance development was considered to be "one of the most remarkable features of the sulphones in leprosy"[75], even inducing researchers to look for new ideas about the mode of action of sulfones against *M. leprae*[107].

Nevertheless, in 1950 Erickson[172] had already reported the relapse of a patient while being on sulfone treatment, and a few years later Wolcott and Ross[173] described some cases of exacerbation of leprosy during sulfone treatment that might have been cases of resistance. Garrett reported in 1955[130] that a few cases led him to suspect its development, and the next year Muir[174], apparently concerned, asked in an editorial in Leprosy Review for extensive information from his readers about suspect cases. The great obstacle to proving resistance was the failure to grow *M. leprae* in the laboratory.

Demonstration. It was not until 1964 that Pettit and Rees[175] were able to experimentally demonstrate sulfone resistant strains of *M. leprae* in three patients. This became possible thanks to Shepard's mouse foot pad technique[176], by which growth of *M. leprae* in the presence of DDS could be demonstrated.

Similar reports soon followed these first findings[177, 178, 179, 180], but the Third Report of the WHO Expert Committee on Leprosy could still state in 1966[152] that fortunately the question of drug resistance to DDS was "not an important one," since it was found "only in a negligible proportion of the cases under treatment." Crawford[181] repeated in 1969 that the frequency of resistance was estimated by Pettit and Rees to be of the order of only 3 per 1000 lepromatous patients, and that "hence as a factor in mass treatment campaigns it was of little significance." Yet, at the same time clear warnings appeared that the low dosages of DDS in favor during these days might greatly enhance the risk of resistance developing[97, 143].

Full doses. The Ninth International Leprosy Congress, held in London in 1968, reflected the ambivalence of the late sixties: on the one hand, enthusiastic reports about effective treatment with 1 mg DDS daily[95], and on the other hand, the apparent need for maintaining relatively high concentra-

[170] Floch, H. Le VI[e] Congrès International de Leprologie. II. Rapport de la commission de thérapeutique; rapport de la commission d'assistance sociale; discussion. Arch. Inst. Pasteur Guyane Fr. et de l'Inini Publ. No. 321, Mars 1954.

[171] Chaussinand, R. and Bourcart, N. Grave relapse of a lepromatous leprosy patient treated for six years with the sulphone J.51. Lepr. Rev. **31** (1960) 116–119.

[172] Erickson, P. T. Relapse following apparent arrest of leprosy by sulfone therapy. Public Health Rep. **65** (1950) 1147–1157.

[173] Wolcott, R. R. and Ross, H. Exacerbation of leprosy during present day treatment. Int. J. Lepr. **21** (1953) 437–440.

[174] Muir, E. Drug resistance in leprosy. Lepr. Rev. **27** (1956) 91–92 (editorial).

[175] Pettit, J. H. S. and Rees, R. J. W. Sulphone resistance in leprosy. An Experimental and clinical study. Lancet **2** (1964) 673–674.

[176] Shepard, C. C. The experimental disease that follows the injection of human leprosy bacilli into footpads of mice. J. Exp. Med. **112** (1960) 445–454.

[177] Adams, A. R. D. and Waters, M. F. R. Dapsone-resistant lepromatous leprosy in England. Br. Med. J. **2** (1966) 872.

[178] Pettit, J. H. S., Rees, R. J. W. and Ridley, D. S. Studies on sulfone resistance in leprosy. I. Detection of cases. Int. J. Lepr. **34** (1966) 375–390.

[179] Rees, R. J. W. Drug resistance of *Mycobacterium leprae* particularly to DDS. Int. J. Lepr. **35** (1967) 625–638.

[180] Shepard, C. C., Levy, L. and Fasal, P. The sensitivity to dapsone (DDS) of *Mycobacterium leprae* from patients with and without previous treatment. Am. J. Trop. Med. Hyg. **18** (1969) 258–263.

[181] Crawford, C. L. The effect of out-patient dapsone in an area of endemic leprosy. Lepr. Rev. **40** (1969) 159–163.

tions in the patient's blood to avoid the development of resistance[182]. The Fourth Report of the WHO Expert Committee on Leprosy, appearing in 1970[183], is another reflection of this ambivalence, but it recommends properly controlled trials to settle the question about high or low doses. Though also in 1973, at the Tenth International Leprosy Congress, held in Bergen, there is no unanimity with regard to the optimum dose[184], it was agreed that inadequate dosage and irregular treatment contribute to sulfone resistance[154, 185]. From now on full doses of 50–100 mg DDS daily were recommended for all lepromatous and borderline lepromatous patients[155, 186, 187, 188], but for tuberculoid or near-tuberculoid patients a maximum of 200–300 mg per week was still advised, since they run a greater risk for nerve damage than for resistance[155].

Finally, in 1977, the Fifth Report of the Expert Committee on Leprosy[80] is very candid about the seriousness of the problem: "Secondary dapsone resistance has become increasingly common throughout the world." The Committee leaves no doubt about the relation between resistance and low doses of DDS, and even bacteriologically negative tuberculoid and indeterminate adult patients should now receive daily doses of 50 mg DDS.

Meanwhile, the situation is growing worse, as is reported from Ethiopia, where recently more than half of 29 patients with previously untreated lepromatous leprosy showed primary dapsone-resistant leprosy[189]. Lechat[168] comments on the historical relation between low doses and resistance as follows: "Nature, through the usual mechanism of evolution, was of course the major culprit. The probability of resistant strains emerging increases with the number of patients treated, the length of treatment, the irregularity of intake, and inversely with dosage. As though nature needed to be assisted, experts advocated in the late 1960's that dosages be reduced, a recommendation for which no rationale can be found and whose result could only be to speed up the emergence of resistance. As a consequence, thousands of lepromatous patients have now been found who suffer from secondary resistance and can no longer improve with dapsone. New patients with primary resistance are reported. Many more patients are in some way incubating resistance, ... In other words, another disease is replacing leprosy caused by *M. leprae*, and for this disease there is no easy cure."

Treatment with combinations of drugs is now recommended for all multi-bacillary cases[80, 190], and leprosy workers are urgently asked to monitor the self-medication of the patients under their care[80]. There need be no doubt that sulfone resistance has definitely closed the discussion about low doses of DDS.

THE MANNER OF USE OF DAPSONE IN TREATMENT

Oral Treatment and Self-Medication in the 1950s

Regular treatment. The WHO Inter-regional Leprosy Conference, held in Tokyo in 1958, apparently considered attendance and treatment to be somehow synonymous. The report of the conference[165] reads: "In discussing what can be understood by reg-

[182] Browne, S. G. Ninth International Leprosy Congress. Some highlights of the week's work. Int. J. Lepr. **36** (1968) 563–570.

[183] World Health Organization. WHO Expert Committee on Leprosy Fourth Report. WHO Tech. Rep. Ser. No. 459, 1970.

[184] Languillon, J. (chairman). Report of Congress Committee 6: Therapy. Tenth International Leprosy Congress. Int. J. Lepr. **41** (1973) 462–465.

[185] Jacobson, R. R. Sulphone-resistant leprosy. Etiology, incidence and treatment in the United States. Int. J. Lepr. **41** (1973) 684.

[186] Pearson, J. M. H., Rees, R. J. W. and Waters, M. F. R. Sulphone resistance in leprosy. A review of one hundred proven clinical cases. Lancet **2** (1975) 69–72.

[187] Waters, M. F. R. (Complications of sulfone therapy). In: *Proceedings of the 1st International Workshop on Chemotherapy of Leprosy in Asia*. Tokyo: Sasakawa Memorial Health Foundation, 1977, p. 135 (discussion).

[188] Jacobson, R. R. (Sulfone therapy of leprosy). In: *Proceedings of the 1st International Workshop on Chemotherapy of Leprosy in Asia*. Tokyo: Sasakawa Memorial Health Foundation, 1977, p. 89–94 (discussion).

[189] Pearson, J. M. H., Haile, G. S., Barnetson, R. St.C. and Rees, R. J. W. Dapsone-resistant leprosy in Ethiopia. Lepr. Rev. **50** (1979) 183–199.

[190] Harris, G. F. Drugs to combat dapsone resistance. Heathrow report. (ILEP No. 1). Colchester, England: LEPRA, 1977.

ular treatment the Conference agreed that a patient conforming to at least 75 per cent of the recommended number of attendances should be considered to be attending regularly." In 1960 the WHO Expert Committee on Leprosy, in its second report[191], took these words about regular attendance even as a definition of regular treatment. In 1966, however, in its third report[152], the Committee twisted the original words somewhat by saying that it agreed "with the criterion established at the WHO Inter-regional Leprosy Conference, Tokyo, 1958, in that a patient taking at least 75% of his prescribed medication is considered to be under 'regular' treatment." Apparently attendance and treatment were no longer synonymous. Only in 1970, in its fourth report[183], the Expert Committee made a straightforward distinction between "regularity of attendance and regularity of treatment." In the 1970s the real impact of this distinction would be shown in many field studies, with the result that patient compliance is now one of the major worries of leprosy workers.

The following review describes how patients and physicians dealt with this phenomenon.

Self-medication in India. With some noteworthy exceptions, such as Cochrane[67, 73, 192] and Molesworth[193], most British leprosy workers promoted the oral route in DDS administration. Of particular importance was the possibility of thereby developing cheap and convenient mass treatment[6, 83].

This does not mean that they all entrusted the patients with tablets for self-administration at home. Thus Lowe[6] wrote about Nigeria: "The giving of the proper doses must be adequately supervised. Primitive people often think that they cannot have too much of a good thing. A big dose of D.A.D.P.S. (DDS), particularly in the early phases of treatment, may be dangerous. Moreover, a patient may be tempted to keep and sell some of his tablets instead of swallowing them."

Muir, working in India, had more confidence in his patients. As early as 1950[83] he mentioned his first experiments with DDS self-medication: "It having been found that in strong, well nourished lepromatous inpatients DDS was well tolerated and could be continued indefinitely without toxic signs, some suitable out-patients were selected and given the drug in 0.2 gm. tablets. To begin with they presented themselves for inspection at weekly intervals and later sometimes every two weeks. It is still too soon to report on these cases, but some of them already show satisfactory clinical improvement. There have been no untoward toxic effects." The next year Muir[139] explained that this system of self-medication has made it "possible to discharge patients who have become bacteriologically negative, whereas in the past it was necessary to retain them as in-patients for a further few years to prevent relapse. On leaving, they are given a supply of 75 tablets, sufficient for 3 months, taking one daily six days a week. They pay the small amount of one rupee eight annas, which helps to ensure that the tablets are actually taken. They are instructed to return for inspection and a fresh supply of tablets after that period."

A few years later, Gilbert[167] also reported from India about DDS self-administration. He had adopted a distance of 20 miles as the limit for attendance to the weekly DDS injection sessions. Those who came from farther away than this were given monthly supplies of DDS tablets. However, "it was with some misgivings that this was done and it was soon realised that a number of patients are not able to understand instructions, especially when it comes to increasing their dose."

In 1956, taking part in correspondence in the International Journal of Leprosy about "the manner of use of DDS in treatment," Wardekar[194] wrote a letter from India concerning 10,000 patients trusted with self-administration of DDS. It is interesting to note that he was not concerned about a little irregularity in the periodical clinic atten-

[191] World Health Organization. WHO Expert Committee on Leprosy Second Report. WHO Tech. Rep. Ser. No. 189, 1960.

[192] Cochrane, R. G. Therapy. In: *Leprosy in Theory and Practice*. Cochrane, R. G. and Davey, T. F., eds. Bristol: John Wright & Sons Ltd., 1959, 203–220.

[193] Molesworth, B. D. (The manner of use of DDS in treatment). Int. J. Lepr. **24** (1956) 202–203 (correspondence).

[194] Wardekar, R. V. Oral DDS treatment by the Gandhi foundation. Int. J. Lepr. **24** (1956) 201–202 (correspondence).

dance among the patients as this was a way of providing "rest periods."

Scepticism in Africa. The BELRA meeting, convened in 1951[70], was apparently worried about the Indian initiatives of its medical secretary, Muir, when it stated: "In the administration of the oral dose twice weekly, the patient should not be given tablets to take away with him unless the physician can trust him to use them according to his instructions, thus preventing serious abuse of the drug. In any case, the importation and distribution of any sulphone drug should be carefully controlled, and its administration supervised by trained medical personnel." Most members of this meeting had their work in Africa, and it appears that indeed only few instances of DDS self-administration can be found on this vast continent during the fifties.

In two extensive reports about visits to a number of African countries in 1952, Cochrane[72, 73] mentions only once an experiment in the distribution of DDS in which District Medical Officers in Kenya were encouraged to give outpatient treatment to all leprosy cases. He says, that this system would be "watched with considerable interest." However, he also notes the scepticism of the sisters at the Tumutumu hospital "as to the tablets being taken regularly after the patients leave the dispensary." Cochrane's own mistrust in self-administration appears when he deals with Northern Rhodesia, being "very surprised" to find that patients had been given DDS tablets to take away with them to a segregation unit, where he "collected a matchbox full of tablets from one patient!" This emphasized "the need for closer supervision, for there were enough tablets in the segregation unit to cause serious ill health, if not death." Even when distribution of DDS was under the direct control of the doctor or sisters fatal accidents could happen, as found in Nigeria: "One patient decided to store the tablets—having pretended to swallow them—until he collected eight 100 mgm. tablets, and took these in one dose. Unfortunately he did not live." In reports of his travels Cochrane also noted the "possibility of a black market in DDS pills" that no system of checking could prevent.

Contributing to the 1956 correspondence mentioned earlier, Davey[195] wrote about the strictly controlled large scale oral distribution of DDS in Eastern Nigeria: "The patient is given his treatment in the presence of witnesses, and takes it then and there. He is not given any to take home." Local centers, segregation villages, and a great number of Leprosy Inspectors formed the basis of this system. Kinnear Brown[196] describes a similar system of strict supervision in Uganda, where "treatment villages" were the corner stone: "If patients could be relied upon to isolate themselves at home and could be trusted with bottles of 50 or 100 tablets, the solution would be simple. Unfortunately, home segregation is an illusion, and even educated people fail to take their medicine regularly." However, he also mentions that "in a few centres patients come fortnightly, taking home with them a supply of tablets for the week they do not have to attend." So self-medication still occurred.

Training of patients. Another contributor to the 1956 correspondence was Beaudiment[197], who in 1953–1954 did an experiment in Cameroon in "training primitive people to take DDS tablets given them." He had European sanitary assistants select among the patients those who seemed "the most intelligent and amenable." They were informed about the aim of daily self-administration, and it was "explained why this favor was a privilege reserved for those who, because of their intelligence, could be trusted to understand the advantages of daily dosage and to follow instructions faithfully. This recognition, given them publicly, flattered those who were selected, and they were careful to take their tablets regularly. During the following weeks the sanitary assistants went without notice to the houses of those patients, asking them to show the tablets they had left. As a rule the number of the remaining tablets corresponded well with the number they should have, which indicated that the plan of daily dosage was being followed. Little by little

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[195] Davey, T. F. Leprosy control in Nigeria. Int. J. Lepr. **24** (1956) 199–200 (correspondence).

[196] Kinnear Brown, J. A. The role of leprosaria and treatment villages in mass campaigns in tropical Africa. Int. J. Lepr. **28** (1960) 1–11.

[197] Beaudiment, R. An experiment with oral DDS in Africa. Int. J. Lepr. **24** (1956) 202 (correspondence).

the other patients, envious of the distinction made in favor of those who were regarded as the most intelligent, requested that they also be given the benefit of the same treatment." However, towards the end of his letter, he smartly remarked that he did not know if the good results had been maintained after his departure, "for Africans are not very persevering people and it is always necessary to wait a long time before success can be claimed."

Long-Acting Injections of DDS

Local circumstances. In India it was shown in 1950 by Dharmendra and coworkers[198], in a study of sulfone blood levels, that the oral administration of DDS twice a week was as good as an intramuscular injection at that interval, if for any reason treatment could not be given daily. Yet, they found a slower fall in blood levels after parenteral administration of the drug. The latter finding makes it understandable that Gilbert[167] chose injections for his once weekly DDS administration, while giving tablets for self-administration at home to those who lived too far away for coming weekly.

It is remarkable in this context, that in francophone Africa a different idea about self-administration, "unfortunately utopian," and the development of really long-acting injections led Lauret and colleagues[199] to do exactly the opposite of what Gilbert did in India: they gave injections to patients who lived far away and tablets to those who could be seen more frequently. This illustrates how new developments and personal ideas played a role in decisions about the manner of DDS administration.

French leprologists. The French went rather far in the development of long-acting DDS injections. Floch and colleagues[76, 82, 200, 201, 202] in Cayenne, French Guiana, drew attention to the retarding effect of larger particles of DDS, suspended in an agar-saline vehicle. With particles of 90–120 μm in diameter injections of 1.5 g every three weeks proved sufficient, and with particles of 200–500 μm they gave a monthly injection of 1.8 g DDS. With the latter, however, the injection needles were often obstructed. In 1956 Floch[202] mentioned that about 10,000 DDS injections had been given by him in the Cayenne dispensary with good therapeutic results.

The French in Africa, with their research center at Bamako[141, 199], suspended DDS particles of 85–95 μm in chaulmoogra acid ethyl esters and gave mostly bimonthly injections of 1.25 g DDS. Though experiments with Floch's suspension had shown a superior retarding effect, the salt in it had a flocculating effect on the agar, and after some months turned that suspension into an irreversible coagulum. At an informal meeting of leprologists, held at Leopoldville in 1954, it was stated that about 47,000 patients in Africa had been put under the injection treatment by the French and the Belgians. Laviron, one of the outstanding promoters of the method, is quoted[141] as saying at that meeting: "The natives love the injections. They are fed up with tablets. That's an argument that counts." Wade[203], discussing the Leopoldville figures, somewhat sceptically remarks that they go "without indication of what proportion of the patients persist with it."

In 1963, i.e., 9 years after the Leopoldville meeting, an extensive report by Giaquinto and Gilbert[142] underlines once more the absolute confidence of French leprologists in the parenteral administration of long-acting DDS suspensions that "should

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[198] Dharmendra, Chatterjee, K. R. and Bose, R. Diamino-diphenylsulphone (DDS) in the treatment of leprosy. Pharmacological aspects. Lepr. India **22** (1950) 174–201.

[199] Lauret, L., Laviron, P., Kerbastard, P. and Jardin, C. Interêt de la chimiotherapie-retard dans la lutte antihansenienne. Int. J. Lepr. **24** (1956) 138–144.

[200] Floch, H. and Gélard, A. M. Utilisation de la DDS-retard en fonction de la grosseur des cristaux de la suspension. Bull. Soc. Pathol. Exot. **47** (1954) 35–40.

[201] Floch, H. Sulfonémies et activités antilépreuses. Arch. Inst. Pasteur Guyane Fr. et de l'Inini Publ. No. 359, Avril 1955.

[202] Floch, H. Injections retard de DDS a "gros grains." Int. J. Lepr. **24** (1956) 145–151.

[203] Wade, H. W. The manner of use of DDS in treatment. Int. J. Lepr. **24** (1956) 189–190 (editorial).

receive a much greater consideration in the planning of the necessary mass-treatment campaigns, to be carried out in large and remote rural areas." After depicting the failures of oral self-medication they note: "Not even the measure of ordering that the previewed daily dosage shall be taken in the presence of the treating staff can be considered a sufficient guarantee: the existence of certain 'black market prices' for the tablets distributed to the leprosy patients and sold illegally by them, at different prices, according to whether some are 'chewed' and others 'unchewed,' is well known to the experienced specialist." They actually "wonder if the leprologists who use the oral treatment only, really believe that the patients concerned are so 'health conscious' in the underdeveloped countries, as to observe their prescription." With some preliminary data they show "the existing possibility of correcting, in a relatively short time, through the use of a correctly applied and well accepted long acting therapy, failures of an oral treatment irregularly followed by unruly patients, under unfavourable conditions."

Experiences elsewhere. De Souza Lima[204], also contributing to the 1956 correspondence in the International Journal of Leprosy, says that in Brazil patients "tolerated the intramuscular treatment for the first few months but later rejected it because it was extremely painful." But he adds: "It appears, however, that some workers now make the injections every fifteen days, in which case the tolerance should be greater."

From Northern Nigeria, Ross[205] remarks: "The injection method could not be used because, for one thing, the people here—unlike those in some places—do not like injections and would not come forward as willingly as they do for the oral treatment." This in sharp contrast not only to the French African Federations, but also to Malaya, where according to Molesworth[193] "the local belief in injections as opposed to mere pills is unbounded."

Ramanujam[206], who worked with Cochrane in India with the first subcutaneous DDS injections, noted that "slow and continuous release of the sulfone from the pockets of deposit under the skin . . . seems to be a definite advantage in dealing with patients of whom a majority tend to be irregular in attendance and to disappear after some time." Apparently, Ramanujam did not consider the possibility of a relation between the injections on the one hand, and the irregularity and disappearance of his patients on the other.

Similarly, Williams and Williams[207] in Uganda, using an intramuscular injection of an aqueous DDS suspension, noted that "the attendance of many . . . had been erratic and not a few had discontinued on their own accord." They added, however: "The alteration to a fortnightly regime has resulted in a more regular attendance and it is hoped that the introduction of appropriate propaganda will achieve even greater continuity."

Cochrane's views. In 1959, in the first edition of Leprosy in Theory and Practice[192], Cochrane made a comparison of the parenteral and oral administration of DDS "by giving 5 marks as a maximum, recording the points so obtained under the following heads: (1) ease of administration, (2) economy of drug, (3) price, (4) pain, (5) effectiveness, (6) reaction producing, (7) toxicity, (8) relapse rate, (9) irregularity of attendance, (10) slowness of absorption, (11) abuse of its use." By so doing, Cochrane noted 38 out of a possible 55 points for the oral administration, and 44 out of a possible 55 points for the parenteral administration.

It is a pity that the "arbiter" does not give any information about details of these scores, but apparently we may count the categories "abuse of its use" and "irregularity of attendance" among the most glorious victories of the final winner of this

[204] De Souza Lima, L. (The manner of use of DDS in treatment). Int. J. Lepr. **24** (1956) 203 (correspondence).

[205] Ross, C. M. DDS treatment in Northern Nigeria. Int. J. Lepr. **24** (1956) 200–201 (correspondence).

[206] Ramanujam, K. Comparison of oral and parenteral DDS treatment. Int. J. Lepr. **24** (1956) 196–197 (correspondence).

[207] Williams, E. H. and Williams, P. H. The story of Kuluva. Lepr. Rev. **24** (1953) 132–138.

game. In Cochrane's words: "The greatest drawback to oral administration . . . is that widespread sulphone therapy encourages abuses which are liable to result in the creation of blackmarkets or other illicit sources of supply. A further obvious drawback to oral administration is doubt as to whether the pill is swallowed when given. It is extraordinary how often one finds patients indulging in tricks in order that the doctor may be deceived into thinking that they have swallowed the drug." And again: "While one accepts oral DDS as a method of choice in large areas of the world I, personally, am convinced that it encourages irregularity of attendance, because the average person will not see why he should walk a considerable distance for the drug when it is only given by mouth, whereas if it is given by injection he feels that it is worth while making the journey."

It was therefore with interest that Cochrane noted "the general trend towards a return to parenteral administration of DDS."

Choice for Oral Treatment

A change. Two things are remarkable about the report of Giaquinto and Gilbert[2], mentioned earlier, in which the confidence of French leprologists in long-acting DDS injections was emphasized so strongly: first, the publication of the report in 1963, and secondly the special mention the authors made of General Richet, as "an epidemiologist with an immense experience in the problems of the control of several tropical diseases, including leprosy." It is namely this Richet who would later on very favorably report[208] about the change to DDS self-administration in that same period and in the same countries of French-speaking Africa.

Apparently, the major initiative had come in 1962–1963 from Dutertre, working in Fada N'Gourma. He analyzed the different methods of DDS administration and reported positively on self-medication during a technical conference at Bobo-Dioulasso in 1964. Others soon followed and came with interesting results from many of the countries under the medical care of the O.C.C.G.E. (l'Organisation de Coordination et de Coopération pour la lutte contre les Grandes Endémies). Speaking about the necessary adaptation to local circumstances, Richet remarks: "Here, the bimonthly injections would still be possible, there, and this has become the rule almost everywhere, the patients prefer henceforth the tablets." Thus the patients had finally become fed up with the injections they had at first loved so much[141]!

This does not say that all French leprologists were immediately won by the new method. So for example Ziegler, director of medical services for the great endemics in Chad, called it a "makeshift." In fact, Richet complains in his report that there is not enough interest in this method amongst the O.C.C.G.E. workers: "It seems that the majority of them from the outset have shown a scepticism towards the methods of self-treatment, which they do not want to change and that prevents them trying the experiment which succeeded so well in other states." It is noteworthy that these words are from a report presented as recently as 1975.

WHO. In the successive reports of the WHO Expert Committee on Leprosy the shift to self-medication is clear. The 1960 report[191] had left the method of administration open to the local circumstances. Tablets should be swallowed under supervision, and if sometimes there was no alternative to self-administration at home, "this should be for as short a period as possible." The 1966 report[152] unequivocally chose oral treatment, though in some situations repository injections might be preferable. The quantity of tablets given to patients at any one time were said to depend upon local circumstances and might "eventually have to be sufficient for three months."

In 1968, however, it was reported in a consultation of leprologists, arranged by WHO[209] that successful WHO-sponsored trials had led in Venezuela to the use of monthly DDS injections in the treatment of

[208] Richet, P. La lèpre. Document de travail présenté à l'occasion de la XVème Conférence Technique de l'O.C.C.G.E. tenue à Bobo-Dioulasso du 7 au 11 avril 1975.

[209] Convit, J., Browne, S. G., Languillon, J., Pettit, J. H. S., Ramanujam, K., Sagher, F., Sheskin, J., De Souza Lima, L., Tarabini, G., Tolentino, J. G., Waters, M. F. R., Bechelli, L. M. and Martínez Dominguez, V. Therapy of leprosy. Bull. WHO **42** (1970) 667–672.

all lepromatous and borderline cases and part of the indeterminate cases of leprosy.

Apparently, this confidence in injections was not shared by the next WHO Expert Committee on Leprosy. The 1970 report[183], reaffirming the choice for oral treatment, goes so far as to warn those who prefer the parenteral method that "the long duration of treatment, the pain that the patient may suffer from the injections, and the possibility of abscess formation should be borne in mind."

All in all, the interest in the parenteral administration of DDS had greatly diminished at the close of the 1960s.

MANAGEMENT OF PATIENT COMPLIANCE

Self-Medication Monitored by Urine Tests

Urine spot tests. As outlined in the previous pages, leprologists have always been aware of the inherent danger of irregularity in DDS self-administration at home. Surprise visits and counting of tablets, as practiced in Beaudiment's experiment in Cameroon in 1953–1954[197], offered a first simple check on drug intake. Endeavors to get more physical certainty about the patient's behavior led to the development of a series of urine spot tests in the 1960s and 1970s.

Colorimetry has been employed for determination of sulfones in body fluids since 1937[5,38], as practiced for sulfonamides[210,211]. There are two basic methods. The first and most widely used is the method of Bratton and Marshall[212]. DDS is diazotized, then coupled with N-(1-naphthyl)-ethylenediamine to form an azo dye. Other investigators have employed this basic method but have used different coupling reagents[38,213]. The second type of method is based on the formation of a Schiff base between DDS and Ehrlich's reagent (4-dimethylaminobenzaldehyde). According to Levy and Higgins[214] this method is 2.4 times more sensitive than the Bratton-Marshall technique.

The reagents were also used to develop colors in paper chromatography, as reported for the Bratton-Marshall reagent in 1949 both by Longenecker[215] and by Smith and colleagues[216], and in 1950 by Boyer and coworkers[217] for Ehrlich's reagent. These color reactions on paper formed the basis for the simple urine spot tests that would be developed to check DDS self-administration.

A first spot test, employing filter paper impregnated with Ehrlich's reagent, was described in 1961 in Brazil by Homem de Mello[218]. The impregnation method was modified by De Castro and colleagues[219], using oxalic acid, nacconol and absolute alcohol, and a higher concentration of Ehrlich's reagent. In 1966, the WHO Expert Committee on Leprosy mentioned this simple urine test to check DDS intake in its third report[152].

The Indian leprologist, Balakrishnan, reported on the possible field applications in 1968[220]. He found that the method could be used for detection of DDS in urine in cases receiving daily doses of 5 mg or above and weekly doses of 25 mg or above. At very low concentrations of DDS, however, the yellow color reaction of urea interfered with the brownish yellow color caused by

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[210] Fuller, A. T. Is p-aminobenzenesulphonamide the active agent in prontosil therapy? Lancet **1** (1937) 194–198.

[211] Marshall, E. K. Determination of sulfanilamide in blood and urine. J. Biol. Chem. **122** (1937) 263–273.

[212] Bratton, A. C. and Marshall, E. K. A new coupling component for sulfanilamide determination. J. Biol. Chem. **128** (1939) 537–550.

[213] Rose, F. L. and Bevan, H. G. L. A new coupling component and simplified method for the estimation of sulphanilamide drugs. Biochem. J. **38** (1944) 116.

[214] Levy, L. and Higgins, L. J. Dapsone assay based on Schiff base formation. Int. J. Lepr. **34** (1956) 411–414.

[215] Longenecker, W. H. Simplified partition chromatographic procedures. Resolution of sulfonamides, sulfones, and their metabolic products from biological materials. Anal. Chem. **21** (1949) 1402–1405.

[216] Smith, M. I., Jackson, E. L., Chang, Y. T. and Longenecker, W. H. Metabolic fate of 4,4′-diaminodiphenylsulfone (DDS) in the rabbit and its isolation from urine. Proc. Soc. Exp. Biol. Med. **71** (1949) 23–25.

[217] Boyer, F., Troestler, J., Rist, N. and Tabone, J. Recherches sur le mode d'activité des sulfones. II. Etude analytique. Ann. Inst. Pasteur **78** (1950) 140–143.

[218] Homen de Mello, P. Método rápido para pesquisas de sulfonamidícos na urina. Rev. Bras. Leprol. **29** (1961) 79–82.

[219] De Castro, I., De Almeida, S. M. and Noqueira de Castro, N. J. Contrôle da absorção de anti-lépricos nas campanhas de saúde pública. Bol. Serv. Nac. Lepra (Rio de J.) **24** (1965) 13–24.

[220] Balakrishnan, S. Application of a spot test for detection of DDS in urine. Lepr. India **40** (1968) 1–5.

the drug. Moreover, as Balakrishnan said, "other medications particularly sulphonamide drugs should be avoided during the period prior to the testing as they will interfere in the test." In a further note on this screening method, Balakrishnan[221] mentions 5% false negative and 5% false positive results in an experiment in which DDS doses ranged from 10 to 75 mg twice a week. In 1972, Noordeen and Balakrishnan[222] described the application of the test under field conditions to 2064 specimens of urine from child contacts of leprosy patients receiving DDS in doses ranging from 10 to 75 mg or placebo tablets. Urine specimens collected before 48 hr following the administration of DDS gave reliable spot tests under field conditions with only few false positives or false negatives.

Another qualitative spot test was published by Peters and colleagues in 1969[223]. They first extracted the urine with ethylene dichloride, evaporated the solvent and dissolved the residue in 50 μl of ethanol, which was then applied to filter paper. DDS was detected with the Bratton-Marshall reagents. Urines obtained up to 24 hr after the ingestion of 10 mg DDS or up to 144 to 168 hr after the intake of 50 mg DDS were routinely positive. There were no false positives. This test was apparently more laborious than the one using the modified Ehrlich's reagent. The literature is remarkably silent about real applications of both tests to check patient compliance in the field.

In the early 1970s Ellard and co-workers[224] studied the relative values of four modifications of spot tests and one quantitative test in which a spectrophotometer was used. In their hands De Castro's test was rather insensitive, since 24 hr after a single dose of 200 mg DDS one third of all urine samples were negative. Preceding extraction greatly improved the sensitivity, such that four days after the 200 mg dose 65% of the urine samples were still positive on the Ehrlich impregnated paper. When extraction was followed by the Bratton-Marshall reaction on a white tile, 68% were positive after four days. In a fourth spot test the unextracted urine specimens were first treated with the Bratton-Marshall reagents and the purple precipitates formed were concentrated as spots on strips of filter paper. This gave only 53% positive results four days after the 200 mg dose.

DDS/creatinine ratios. In Ellard's quantitative method the ratio of DDS plus its diazotizable metabolites (Bratton-Marshall technique) to creatinine (sodium picrate coloring) in the urine is determined by spectrophotometry. By relating the quantity of diazotizable material to that of creatinine the influence of diuresis is largely eliminated. With this method 65% of urine samples were found DDS positive four days after a 200 mg dose, which is not better than the percentage obtained with two of the four spot tests. However, after daily dosage with not more than 25 mg DDS it is the only method giving 100% positive results. It was concluded that quantitative determination of the DDS-creatinine (D/C) ratio discriminates more efficiently between urine samples from patients and controls than the four qualitative methods investigated.

Application of this D/C method to monitor daily DDS intake of leprosy patients in Malawi was described by Ellard and colleagues in 1974[225]. Results showed that the patients attending the mobile clinics had taken only about half of their prescribed DDS doses in the days immediately preceding their attendance. It was found that this overall picture of compliance in the group could also be obtained by determining the D/C ratio in a pool of equal volumes of the individual urine samples, using a fluorimetric DDS determination[226]. This might in

[221] Balakrishnan, S. A note on the screening for DDS in urine by spot test. Lepr. India **41** (1969) 77–78.

[222] Noordeen, S. K. and Balakrishnan, S. Spot test for DDS (diamino diphenyl sulphone) in urine under field conditions. Indian J. Med. Res. **60** (1972) 367–371.

[223] Peters, J. H., Lin, S. C. and Levy, L. A rapid qualitative spot test for the detection of dapsone in urine. Int. J. Lepr. **37** (1969) 46–51.

[224] Ellard, G. A., Gammon, P. T., Helmy, H. S. and Rees, R. J. W. Urine tests to monitor the self-administration of dapsone by leprosy patients. Am. J. Trop. Med. Hyg. **23** (1974) 464–470.

[225] Ellard, G. A., Gammon, P. T. and Harris, J. M. The application of urine tests to monitor the regularity of dapsone self-administration. Lepr. Rev. **45** (1974) 224–234.

[226] Ellard, G. A. and Gammon, P. T. A fluorometric method for the simultaneous determination of 4,4′-diaminodiphenyl sulfone (DDS), N-acetyl-DDS (MADDS) and N,N′-diacetyl-DDS (DADDS) in serum or urine. Int. J. Lepr. **37** (1969) 398–405.

forthcoming cases be done as a pilot experiment before deciding to study individual D/C ratios colorimetrically in order to indicate which patients were likely to be the most serious defaulters in self-medication. The authors point to it that, "because of the slow elimination of DDS from the body and the large range of DDS/creatinine ratios found in urine samples from different patients receiving the same daily dose of DDS, the result of a single urine test cannot establish conclusively whether or not a particular patient actually took the prescribed dose."

The D/C method was soon used in other leprosy endemic areas, and the extent of the noncompliance with DDS self-administration became apparent. Among groups of patients in Ethiopia[227], Tanzania[228], Burma[229, 230] and India[231, 232, 233, 234] the situation proved to be as bad as, or even worse than in the Malawi study. Interestingly, Balakrishnan[231] found a markedly higher irregularity of DDS intake in the biweekly as compared with the daily dosage schedule. There were some positive reports too. Thus Jesudasan and colleagues[235], working in Gudiyatham Taluk in India, found that 96.1% of the 50 mg doses and 79.3% of the 100 mg doses were faithfully taken. Huikeshoven and Bijleveld[236] found a faithful weekly self-administration of DDS among a group of patients in Kenya who were assisted by a highly motivated leprosy field worker. A recent report came from Balakrishnan and Christian[237], who monitored compliance in Tamil Nadu among groups of outpatients on doses of 100 mg DDS, most of them for 6 days and the rest for 3 or 4 days in a week. In this study the estimated irregularity of drug intake ranged only from 15 to 25%. The Table summarizes the findings in the reports mentioned.

All in all, the D/C method has now affirmed for leprosy control what Fox[238] wrote 20 years earlier about anti-tuberculosis campaigns: "Surprisingly, mere attendance at the clinic in no way means regularity in taking medicine."

Factors in Non-Compliance

Patients' expectations. That the treatment compliance in leprosy is not worse than in other chronic diseases is apparent from a comparison of the D/C estimations with a great number of other compliance studies, extensively reviewed in 1976 by Sackett and Haynes[239]. Naturally, this should be no argument to accept the situation.

For improvement it will first of all be necessary to understand as much as possible of the leprosy patients' behavior towards treatment delivery. As for their motivation, it is likely that what the WHO Expert Committee on Leprosy said in its fifth report[80] is correct: "A situation in which patients are required to maintain treatment for many years may lead to a loss of motivation." There are, of course, many more factors

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[227] Low, S. J. M. and Pearson, J. M. H. Do leprosy patients take dapsone regularly? Lepr. Rev. **45** (1974) 218–223.

[228] Huikeshoven, H. C. J., Honhoff, C., Van Eys, G. J. J. M., Anten, J. G. F., Mayer, J. M. A. and Van Helden, H. P. T. Weekly self-medication of leprosy patients monitored by DDS/creatinine ratios in urines. Lepr. Rev. **47** (1976) 201–209.

[229] Gyi, K. M., Lwin, M. M., Myaing, Y. Y., Oo, K. M. and Shwe, T. Reliability of dapsone self-administration by leprosy patients in the Rangoon area. Lepr. Rev. **49** (1978) 283–286.

[230] Hagan, K. J., Smith, S. E., Gyi, K. M., Lwin, M. M., Myaing, Y. Y., Oo, K. M., Shwe, T., Tin, K. M., Than, K. N., Hla, T. and Kywe, W. W. The reliability of self-administration of dapsone by leprosy patients in Burma. Lepr. Rev. **50** (1979) 201–211.

[231] Balakrishnan, S. Monitoring self administration of dapsone by patients. Lepr. India **49** (1977) 364–371.

[232] Naik, S. S. and Ganapati, R. Regularity of dapsone intake by leprosy patients attending urban treatment centre. Lepr. India **49** (1977) 207–215.

[233] Naik, S. S. Irregularity of dapsone intake in infectious leprosy patients attending an urban treatment centre. Its magnitude and causes. Lepr. India **50** (1978) 45–53.

[234] Nigam, P., Siddique, M. I. A., Pandey, N. R., Awasthi, K. N. and Sriwastava, R. N. Irregularity of treatment in leprosy patients. Its magnitude and causes. Lepr. India **51** (1979) 521–532.

[235] Jesudasan, K., George, B., Chacko, C. J. G., Taylor, P. M., Kurian, P. V. and Job, C. K. An evaluation of the self administration of DDS in Gudiyatham Taluk. Lepr. India **48** (1976) 668–676.

[236] Huikeshoven, H. and Bijleveld, I. Encouraging results from DDS urine analysis among registered leprosy patients in the Wangas, Kenya. An exception that challenges the rule. Lepr. Rev. **49** (1978) 47–52.

[237] Balakrishnan, S. and Christian, M. Assessment of self-administration of dapsone in urine by out-patients attending field clinics. Lepr. India **51** (1979) 568–569.

[238] Fox, W. The problem of self-administration of drugs. With particular reference to pulmonary tuberculosis. Tubercle **39** (1958) 269–274.

[239] Sackett, D. L. and Haynes, R. B., eds. *Compliance with Therapeutic Regimens*. Baltimore and London: Johns Hopkins University Press, 1976.

THE TABLE. *DDS/creatinine estimations of leprosy patients' compliance with DDS self-medication.*

Reference	Country	Patients	Dosage	% doses taken[a]	% regular in treatment[a]
Ellard, *et al.*[251]	Malawi	mobile clinic, out-p.	25 mg daily	53	30
Low and Pearson[227]	Ethiopia	urban clinic, out-p.	25–100 mg daily	42	—
Huikeshoven, *et al.a*[228]	Tanzania	rural clinic, out-p.	300 mg weekly	50	—
Jerudasan, *et al.*[235]	India	rural clinic, out-p.	50–100 mg daily	87[b]	72[b]
Balakrishnan[231]	India	urban clinic, out-p.	25–100 mg daily	59[b]	52[b]
			25–200 mg bi-weekly	51[b]	25[b]
Naik and Ganapati[232]	India	urban clinic, in-p.	10–100 mg daily	—	77
		urban clinic, out-p.	10–100 mg daily	—	57
Naik[233]	India	urban clinic, out-p.	no data	—	51
Huikeshoven and Bijleveld[235]	Kenya	rural clinic, out-p.	300 mg weekly	84[b]	—
Gyi, *et al.*[229]	Burma	urban clinic, in-p.	50 mg daily	82	—
		urban clinic, out-p.	50 mg daily	84[b]	—
Hagan, *et al.*[230]	Burma	rural clinic, out-p.	50 mg daily	42[b]	—
		urban clinic, out-p.	25–100 mg daily	74	—
Nigam, *et al.*[234]	India	urban/rural clin., out-p.	50–100 mg daily	24	—
		urban clinic, out-p.	no data	—	48
Balakrishnan and Christian[237]	India	rural clinic, out-p.	100 mg daily	—	80[b]

[a] Some authors describe their results in terms of estimated percentages of DDS doses actually being taken. Others present the estimated percentages of patients taking treatment regularly. Note that not all authors define "regular treatment" similarly.

[b] Calculated from data presented in article.

that influence the patients' motivation. Thus Browne[240] had "the terrible experience of opening the lockers of the patients hospitalized and finding 20 unopened bottles of rifampicin. Rifampicin having been prescribed by the doctor in good faith but never having been taken by the patients because they wanted to remain in that leprosarium." The observation of Koticha and Nair[241] that "more of the patients who are beggars are deformed and irregular than any other class of patients," may have a similar background of lack of motivation to be cured.

In 1977, Bijleveld[242] made a thorough study of the expectations and experiences of leprosy patients in part of Kenya. In his report he points out that "for patients who believe, or even merely suspect that their leprosy could be caused by spirits, or witchcraft, modern treatment is at best a holding operation, promising temporary relief not a cure; and therefore regularity of attendance is not urgent." Low and Pearson[227], trying to find possible explanations for the irregular DDS intake they found in Ethiopia in 1974, gave as first suggestion that "the patients are sharing out or selling some of their tablets." The suspicion of sharing DDS with others was also heard by Bijleveld in his contacts with experienced Kenyan leprosy workers: "You can never trust a human being that has a family and is suffering from a disease. They will protect the family."

Black market. It seems to be common knowledge among leprologists that tablets are sold by some patients, even when they are chewed[142, 243]. As early as in 1955 Garrett[130], working in Nigeria, spoke about "a

[240] Browne, S. G. (Non-sulfone drugs in the treatment of leprosy). In: *Proceedings of the 1st International Workshop on Chemotherapy of Leprosy in Asia.* Tokyo: Sasakawa Memorial Health Foundation, 1977, p. 167 (discussion).

[241] Koticha, K. K. and Nair, P. R. R. Treatment defaulters in leprosy. A retrospective study of 42,000 cases. Int. J. Lepr. **47** (1979) 50–55.

[242] Bijleveld, I. Leprosy care: patients' expectations and experience. A case study in Western Province, Kenya. Amsterdam: Royal Tropical Institute, 1977.

[243] Warren, G. Clinical assessment and management of dapsone-resistant leprosy for the field worker. Lepr. Rev. **48** (1977) 113–121.

wide illicit trade in dapsone as in all successful medicines in this country." Naturally, the patients are not the only "illicit traders." Bijleveld[244], who also did some fieldwork in Nigeria, was assured by people in ministerial jobs that "half the UNICEF supply of DDS for Northern Nigeria was not needed to meet the demands of clinics, and indeed 'vanished' to reappear for sale elsewhere." He himself "witnessed leprosy attendants during clinics giving registered patients fewer pills than they should be receiving, writing down the full dose in their registers." The suggestion is clear! As regards the local trade he notes: "For most who want to buy pills, local markets provide the opportunity. Traveling salesmen carry DDS to villages as well. Beggars, deformed from leprosy, are a door-to-door supply."

Preference to buy DDS in the black market can have various motives. In his Nigeria report Bijleveld noted: "Certain patients spoke of disillusioning experiences when they tried to register for official treatment and the leprosy attendant demanded a bribe. Aware that bribes may have a beginning but no end, they decided to secure their supply of DDS from elsewhere. Others felt 'ashamed to go as a leper and stand in line to get medicine' . . . . Furthermore, patients who knew they had leprosy but declined to pay clinic visits told us that, whereas clinics made travel necessary which cost working time, DDS could be purchased nearby. For some, secrecy may have influenced their preference . . . . Finally, many who bought DDS on the 'black market' had explanations for their conduct on the order of 'that is our primitive way of life,' 'wherever we hear of health, we go.' Purchase of DDS also protects a patient from the risk of rude treatment from health personnel: 'sometimes because you are from the bush they send you away.' "

Bijleveld, however, criticizes the hypothesis that the "black market" might have been a leading contributing factor to reduced leprosy prevalence in Nigeria, and he points out certain dangers inherent in it:

1) "All that is sold on the 'black market' as DDS, is not what it pretends to be . . . .
2) At least some pills sold by black marketeers are likely to have been held back from registered patients who are entitled to them . . . .
3) DDS salesmen are unlikely to know, or care about the proper dosage of the pills for their clients . . . .
4) The most important, and dangerous effect of the 'black market' in terms of leprosy control, however, seems to me that irregular, unsupervised use of DDS can lead to increased drug-resistance."

To illustrate these dangers and to show the actual problems individual patients may be coping with, here follow parts of two case-reports noted by Bijleveld in Kenya. Similar cases are likely to be found in most other leprosy endemic areas.

The first deals with a school teacher, 26 years of age, with fixed contractures of the fingers of one hand and prominent lesions on his face, trunk, thighs and upper arms: ". . . as a child the boy had been taken by his father for leprosy treatment at a tree clinic where he received DDS irregularly for a number of years before defaulting. Years later when the boy had a first 'non-qualified' teaching position at a primary school, he acquired a private supply of DDS from an 'understanding' leprosy fieldworker. Within two years spreading lesions and trouble with his hands—despite his supply of DDS—brought him to consult medical advice. His father took him, for a second time, to a traditional leprosy specialist. On his own initiative the teacher went to a private clinic where the doctor informed him that he was suffering from vitamin deficiency! . . . For years, while his leprosy grew progressively more serious, he kept taking vitamins as if expecting them to cure him."

The second case concerns a patient of 28 years, called Peter, who was rushed to the leprosy hospital at Alupe because of a serious reaction: ". . . Peter's recovery from reaction had been so swift that after a week in Alupe he wanted to go home. Explanations about how steroids worked, and why to go home too soon could be dangerous,

[244] Bijleveld, I. An appraisal of diverse actual and potential public health activities in Kaduna State, Northern Nigeria. A report on fieldwork May–July 1977. Amsterdam: Royal Tropical Institute, 1977.

were less convincing than the appearance of restored health . . . . When he tried to rejoin his tree clinic without an Alupe letter of discharge, LFW A (leprosy fieldworker A) followed guidelines and refused him treatment. Peter was prepared for this possibility. He had bought a tin of DDS from a Luo in Alupe and continued giving himself ¼ pill daily until his supply ran out. Complaints were returning to hands and feet, when LFW A sent word to Peter he could now rejoin the clinic."

Fieldworker. There is a general agreement that the quality and nature of the physician-patient relationship is important in compliance[245]. This may count even more for the relationship between fieldworker and leprosy patient. Varkevisser[246], who studied the integration of combined leprosy and tuberculosis services in Kenya, notes that "failure of a person who hands out DDS to turn up at a tree clinic for some months in succession may so thoroughly dishearten patients that some never return." Or more positively in Bijleveld's words: "The cardinal lesson LFW A taught me was that when the fieldworker is regular, his patients are also."

The influence of these paramedical workers on the patients' behavior can hardly be overestimated. They are not just the distributors of DDS but also the obvious persons to motivate the patients by health education. The importance of this exercise for the promotion of compliance may be surmised from Jacobson's experience in Carville[188]: "Prior to 1970, a review of the records indicated that, probably, no more than 50% of the prescribed medication was being taken. At that time, we spent some time in the area of patient education trying to make patients aware of why they were being treated, what kind of problems they are going to have if not treated, and what kind of long term benefits there might be. We also, at that time, switched from the broken schedule of dapsone administration to a daily schedule. It was an important change in getting the patient to take their medication regularly."

Also Naik[233], who studied the magnitude and causes of the irregularity of DDS intake in Bombay, stresses the value of "frequent educative talks," and an analysis of the reasons for defaults of leprosy patients in Kanpur led Bhagoliwal and colleagues[247] to the conclusion that "the retarding effect on attendance of the majority of reasons . . . can be minimised to a considerable extent through effective and constant interpersonal motivation and adequate health education." Nigam and co-workers[234], who recently studied the problem in another area of India, came to similar conclusions.

Recent Developments and Recommendations

Fully supervised intermittent chemotherapy. The disappointing result of the first D/C estimations of leprosy patient compliance, by Ellard and colleagues in 1974[225] in Malawi, induced those workers to remark that "the only practical response to a serious overall level of defaulting might be to consider replacing unsupervised daily chemotherapy by some form of 'fully supervised' intermittent chemotherapy."

For some leprologists the 2½ or 3 monthly injection of 225 mg di-acetylated DDS (DADDS), especially propagated by Shepard's group of workers[248], seemed to be the answer. In Richet's words[208]: "It might perhaps approach that 'miracle-medicament' we are waiting for since twenty years." Unfortunately, in our days of increasing incidence of sulfone-resistance, this miracle-medicament cannot be accepted to replace DDS tablets, because of the very low blood levels (50 ng/ml) sustained by it. It is, however, justified by the WHO Expert Committee on Leprosy in its fifth report[80], and

[245] Gillum, R. F. and Barsky, A. J. Diagnosis and management of patient noncompliance. JAMA **228** (1974) 1563–1567.

[246] Varkevisser, C. M. Integration of combined leprosy and tuberculoid services within the general health care delivery system Western Province, Kenya. Amsterdam: Royal Tropical Institute, 1977.

[247] Bhagoliwal, A., Chandra, J. and Mishra, R. S. Some observations on default among leprosy patients. Lepr. India **51** (1979) 96–102.

[248] Shepard, C. C., Tolentino, J. G. and McRae, D. H. The therapeutic effect of 4,4′-diacetyldiaminodiphenylsulfone (DADDS) in leprosy. Am. J. Trop. Med. Hyg. **17** (1968) 192–201.

by individual authoritative leprologists[249,250,251], as a booster supplement to daily DDS self-administration.

It is interesting to note that Koticha and Nair[241], in a recent paper from Bombay, reject DADDS for the very same property that makes it so attractive to others: its long action! They have the impression (once cherished so much by the French), that "parenteral therapy is more appreciated than oral therapy in a serious disease like leprosy, particularly by uneducated patients. It is felt that more regularity is then assured." They point to it however, that "long-acting injections of DADDS (once in 77 days) cannot have the psychological advantage of weekly or fortnightly injections." In this regard the observation of Bijleveld[242] should be mentioned that "DDS will not impress newly registered leprosy patients . . . . Who can be expected to believe that ¼ of a white tablet each week, or later, even a maximum of three whole tablets a week will be adequate to combat a disease as 'strong' as leprosy?" Even now that whole tablets are taken daily right from the beginning, it is worthwhile to keep an open mind for a local preference of injections.

A rather drastic possibility of "fully supervised intermittent chemotherapy" is the implantation of DDS incorporated in silicone rubber, as investigated by Antia and Bundeally. In a preliminary report in 1974[252], they noted blood levels of 0.5–1 μg/ml for 150 days after implantation of DDS in rabbits, be it subcutaneously or intraperitoneally. In a second preliminary report, published two years later[253], it was shown that small amounts of DDS were excreted in a rabbit's urine for over a year after the subcutaneous implantation of 55 mg DDS/kg body weight. The study is being continued.

Wheat flour and rice grains. In 1977, Naik and Pandya[254] investigated in India the possible addition of DDS to wheat flour. Provided the usual number of "chapatties" is consumed, 400 mg DDS/kg wheat flour will give blood levels corresponding to full doses of DDS. They concluded their paper saying: "The acceptability of this mode of administration of drug has to be tested in families of infectious leprosy patients, where chemoprophylactic and therapeutic considerations are important." It is not known how far Naik and Pandya have progressed in this.

Recently, Japanese workers[255] reported studies on the adsorption of DDS to rice grains. Their results are reported as showing the probable absorption from the stomach wall of DDS annexed to these grains. Apparently, they consider the possible use of the artificial DDS-rice for chemoprophylaxis of leprosy.

It is unlikely that indiscriminate large scale distribution of DDS in food products will be readily accepted by leprologists and public health authorities. This is because of the risks of allergic reactions, toxic effects, and the further development of sulfone resistance.

Field-test needed. The previous pages have shown that the satisfactory form of "fully supervised intermittent chemotherapy" has not yet been found. Self-administration of DDS is indicated in most leprosy control programs. It has also been made clear that a check on drug intake is not superfluous. Ellard's D/C urine test has

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[249] Rees, R. J. W. Combined therapy in principle and practice for the control of dapsone resistance. Lepr. Rev. **49** (1978) 97–100 (editorial).

[250] Wheate, H. W. Dapsone resistance in patients with treated lepromatous leprosy. Lepr. Rev. **50** (1979) 252–259 (correspondence).

[251] Ellard, G. A. Pharmacological aspects of the chemotherapy of leprosy. Lepr. Rev. **46** (1975) (Suppl.) 41–51.

[252] Antia, N. H. and Bundeally, A. E. Prolonged release of 4,4′-diaminodiphenylsulphone (DDS) by incorporation in silicone rubber. A preliminary report. Int. J. Lepr. **42** (1974) 58–62.

[253] Panthaki, M. H., Desai, A. C., Bhide, M. B. and Antia, N. H. Absorption of 4,4′-diaminodiphenyl sulfone (DDS) by incorporation in silicone rubber. Lepr. India **48** (1976) 138–141.

[254] Naik, S. S. and Pandya, S. S. Dapsone in wheat flour as a possible method of therapy in leprosy. A laboratory report. Lepr. India **49** (1977) 516–520.

[255] Gidoh, M., Sakamoto, Y., Tsutsumi, S., Funazu, T., Koide, A. and Narita, M. Trials for chemoprophylaxis of leprosy by DDS. Fundamental studies on an artificial DDS-rice. Jap. J. Lepr. **48** (1979) 1–6.

met a demand in many leprosy centers. Nevertheless, it is not the "simple but sensitive spot test" waited for by the man in the field.

In A Guide to Leprosy Control (an informal document of the WHO, edited in 1979) the need for such a test is once again stressed. None of the tests devised so far is considered completely satisfactory, but an unpublished modification of the Bratton-Marshall technique is tentatively recommended by the compiler of the Guide. The modification devised by Seydel makes use of four impregnated filter papers. It looks simple enough, but this technique will inevitably show its disadvantage of cross-reactions with diazotizable substances in the urine, and it remains to be seen whether it will be any better than earlier spot tests.

In 1977 Ellard and Greenfield[256] proposed to add an easily detectable marker to drugs prescribed for self-administration. They think in this respect of isonicotinic hydrazide (INH). The question is whether it will be acceptable to add this to drugs such as DDS.

Moulding[257] recently suggested to leprologists to introduce his "medication monitor," a specially designed dispenser containing a minute amount of radioactive material and photographic film to record the regularity with which medication is removed. However, as he himself remarks, "the patient may remove medication regularly to create a good film record but ingest none of it." One may moreover wonder whether it will be a simple thing to distribute DDS henceforth in these dispensers.

All in all, an ideal field test for DDS has not yet been developed, notwithstanding the urgent need for one. Therefore it seems appropriate to end this review with words from the last sentence of the fifth report of the WHO Expert Committee on Leprosy[80]: "Simpler methods for analysing urine for dapsone content are required."

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[256] Ellard, G. A. and Greenfield, C. A sensitive urine-test for monitoring the ingestion of isoniazid. J. Clin. Pathol. **30** (1977) 84–87.

[257] Moulding, T. S. The potential uses of the medication monitor in the treatment of leprosy. Int. J. Lepr. **47** (1979) 601–606.

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Dr. Ernest Marchoux
President of the International Leprosy Association
1938–1942

Editor's Note: The above photograph was not available in time for the March issue (49/1, p. 72)—RCH