SULFONE THERAPY OF LEPROSY BACKGROUND, EARLY HISTORY AND PRESENT STATUS¹

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A discussion of the sulfone therapy of leprosy is appropriate as a part of program devoted to the memory of Paul Ehrlich, for it was the work of Ehrlich which guided and stimulated the succeeding generation to develop the sulfones and to prove their value.

The first published report on the treatment of leprosy with a sulfone was that of Faget *et al.* (²³) of the Public Health Service Hospital at Carville, La., in 1943. This dealt principally with Promin, and marked the first major change in the chemotherapy of leprosy since the ethyl esters of chaulmoogra oil were used by McDonald and Dean (⁴²) in 1918. When large-scale controlled trials of the sulfones established beyond doubt their value in lepromatous leprosy, their introduction became a historical event of major importance in modern medicine. The chain of circumstances which led to their use is therefore of more than ordinary interest.

USE OF 4,4'-DIAMINODIPHENYL SULFONE (DDS) IN STREPTOCOCCAL INFECTIONS—AND ITS ABANDONMENT

Following Domagk's (¹⁶) epoch-making discovery of the therapeutic value of Prontosil (diaminoazobenzene-4'-sulfonamide) in streptococcal infections, and the supplemental finding by Tréfouël *et al.* (⁵³) that the activity of Prontosil was parallel to that of *p*-aminobenzene sulfonamide, later designated "sulfanilamide," many compounds of this series were tested in a search for substances of broader therapeutic spectrum and lower toxicity. None showed notable superiority over sulfanilamide. The area of exploration was therefore widened to include drugs of the sulfone class. These differ in chemical structure from the sulfonamides in that the sulfonyl radical is combined with two carbon atoms whereas in the sulfonamides this radical is combined with one carbon atom and an amino group.

The first sulfone to be tested biologically was 4-4'-diaminodiphenyl sulfone (p,p'-sulfonyldianiline, Dapsone), commonly called DDS, which has an amino group combined with each benzene ring in the para position. The synthesis of DDS had been reported by Fromm and Wittmann (³³) in 1908, the same year in which Gelmo (³⁴) had reported the synthesis of *p*-aminobenzene sulfonamide.

¹Modified from a paper read August 17, 1960, at the annual meeting held in Washington, D. C., of the American Institute for the History of Pharmacy, Section II: Program in honor of Paul Ehrlich.

²The author died on April 6, 1963.-EDITOR.

The story of DDS in medicine begins in 1937. Buttle *et al.* (*) in England and Fourneau *et al.* (*) in France tested this drug and some of its derivatives against experimental infections in mice. They found that it would effectively suppress streptococcal infections in doses of only 1/100th of those required of sulfanilamide. It proved, however, to be about 25 times as toxic. The following quotation from the article by the French workers cited is an example of international cooperation of the highest type:

"Notre ami Dr. Buttle (The Wellcome Physiological Research Laboratories) nous à fait part des expériences qu'il a enterprisés tout a fait indépendamment des nôtres sur les derivés de la diphenylsulfone; les résultants expérimentaux qu'il obtenus se montrent dans leur grandes lignes comparables aux nôtres et c'est an plein accord avec lui que nous publions cette note en France au moment où lui-même a rapporté en Angleterre ses propres résultats. Il a essaye egalment le derive amine correspondant, la diamino-4-4' diphenylsulfone, qui s'est montré, comme nous avons pu le constater nous-mêmes, à la fois plus active et plus toxique."

In 1939, Rist (⁴⁸) of the Institut Pasteur found that DDS had, *in vitro*, a much stronger bacteriostatic effect than sulfanilamide against both human and avian tubercle bacilli, and in the same year Rist *et al.* (⁴⁹) reported favorable results with DDS in experimental infection of the rabbit with the avian tubercle bacillus (the so-called Yersin tuberculosis).

The first reports of the clinical use of a sulfone derivative in man were made by Heitz Boyer *et al.* (³⁶) and by Palazzoli and Bovet (⁴⁶). These articles, published in 1937, dealt with the action of *p*-diacetylaminodiphenyl sulfone (1399 F), a disubstituted compound, in the treatment of gonorrhea. The results were as favorable as those obtained with a sulfonamide (1162 F). With doses as large as 3 gm. daily, continued for 10 to 20 days, signs of intolerance were observed only exceptionally and were always benign and transitory.

In a careful search of the literature I have been unable to find any concurrent report of the treatment of streptococcal or other infections of man with DDS between 1937 and 1940 except for the statement of Feinstone *et al.* (²⁴) in 1938 that "toxicity in our experience precludes its use in human beings." In 1950, P. H. Long (³⁹), a prominent American worker on the sulfonamides and a coauthor of the paper by Feinstone and associates, recalled that "about four patients suffering from acute bacterial endocarditis had been treated with doses at a somewhat lower level than we had found effective in mice." In each case treatment had to be discontinued within a few days because of anemia.

In 1950, also, Brownlee (⁴), another early worker on the sulfonamides and sulfones, gave what he called "one answer to the question of how the belief got established that DDS is so terribly toxic."

It will be recalled that DDS was discovered before sulphapyridine or sulphathiazole

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or any of the later sulpha drugs which proved to be effective in pneumonia. As soon as the efficiency of DDS against pneumococci in animals was discovered in these laboratories here [Wellcome Laboratories], that substance was pressed into service in man. The blood level which was necessary to eliminate the pneumococcus in animals, i.e., somewhere about 5 to 7.5 mgm. per cent, is indeed toxic for man-terribly toxic. Doses of 1 to 3 gm. daily produced an acute hemolytic crisis on the third day, followed later by signs of central (cerebral) irritation. The pneumonia appeared to be successfully aborted.

Recently (1960) Professor Buttle told me of a similar experience of one of his colleagues who used DDS during this early period in doses of about 1 to 2 gm. daily. Alarming toxic reactions followed.

Thus it was that DDS was introduced-and abandoned-as a chemotherapeutic agent in human infections without having been tried in either tuberculosis or leprosy. The ensuing search for a related compound of lower toxicity led to the synthesis of a number of disubstituted derivatives. Except for Compound 1399 F, the first of these to be used in man was Promin.

EVENTS WHICH LED TO THE TRIAL OF PROMIN IN LEPROSY

Sharp and Payne (50) relate that Promin, 4,4'-diaminodiphenylsulfone-N,N' di-(dextrose sodium sulfonate) was synthesized on August 6, 1937, by Tillitson in the laboratories of Parke, Davis and Co. In April 1939 a report was published of a trial of Promin in experimental pneumonia in mice by Grecy et al. (35). 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. Early in 1940 a brief report was made by Cowdry and Ruangsiri (13) of its trial in experimental infection of the rat with Mycobacterium leprae murium (so-called rat leprosy).³

According to Dr. W. H. Feldman (personal communication), a supply of Promin for clinical trials in postoperative infections and for studies of experimental tuberculosis was obtained by Dr. H. C. Hinshaw of the Mayo Foundation from Dr. E. A. Sharp of Parke, Davis and Co. The tuberculosis studies were commenced on May 4, 1940, and carried out along lines followed in previous work with sulfapyridine (²⁵). It was the preliminary report by Feldman et al. (²⁶) of the effectiveness of Promin in experimental tuberculosis in the guinea-pig, published in October 1940,⁴ which led directly to the use of the sulfones in leprosy. The sequence of events was as follows:

The results at the Mayo Foundation came to the attention of Dr. G. H. Faget, medical office in charge at the Carville leprosarium, who had

³As is mentioned later this study, which was a search for sufficient evidence of antimycobacterial action to warrant a trial in leprosy, was suggested by Dr. Walter M. Simpson. ⁴An Associated Press dispatch from Rochester, Minnesota, dated November 22, 1940, giv-

ing a summary of this report, appeared in the New York Times and other newspapers.

long been a student of tuberculosis. There followed an exchange of letters between Dr. Faget and Dr. Sharp, then director of the Department of Clinical Research of Parke, Davis and Co. Copies of these letters have been made available by Drs. Sharp and L. A. Sweet, the latter, vice president of Parke, Davis and Co., and are reproduced here in chronological order.

1. Dr. Faget to Dr. Sharp, December 9, 1940 (see Fig. 1):

I have noted with a great deal of interest the work done at the Mayo Clinic with chemotherapy in experimental tuberculosis in guinea pigs. They seemed to obtain the best results with one of the sulfonamide drugs which was supplied through the courtesy of Parke Davis and Company. The name of this preparation was "Promin."

Will you please inform me if any other experimental work has been done with this drug in acid-fast diseases to determine its value, as well as its relative toxicity? If so, we would like to try it at the U. S. Marine Hospital, Carville.

Any literature which you can send us on "Promin" would be appreciated.

2. Dr. Sharp to Dr. Faget, December 18, 1940 (see Fig. 2):

I have your letter of December 9th referring to the work of Feldman and Hinshaw, of the Mayo Clinic, on diaminodiphenyl sulfone, Promin, in experimental tuberculosis.

The Mayo publication is the only report that has been made although comparable results were obtained in a local institution shortly after general investigation of the drug was initiated about two years ago. Dr. E. V. Cowdry, of Washington University, St. Louis, has made a study of Promin in rat leprosy but to date I do not know the outcome of his observations. I have no doubt that he would be willing to discuss the subject with you.

As to the use of Promin in the human subject, the route of administration has been limited to the parenteral, particularly intravenously, during the past eighteen months. Due to the effect of hydrochloric acid, free sulfone is liberated in the human subject when it is given orally with consequent increase in toxicity. In dynamic infections we have been giving 12 to 15 Gm. in divided doses within 24 hours by the intravenous route with negligible manifestations of toxicity or detrimental effect on the hemopoietic system. Many thousand doses have been given and these data have been reported to the Federal Security Administrator with the expectation that the drug will be approved for release.

A description of Promin without the final summary of clinical experience submitted to the government is attached herewith. I would not recommend the oral use of the drug in leprosy for the reasons stated above. If you elect to try it after reviewing the description, however, the ampoules can be supplied. A copy of this letter is being sent to Dr. Cowdry with an appropriate letter of transmittal, which I trust will be the means of initiating an exchange of correspondence between you.

Awaiting with interest further developments and assuring of my willingness to cooperate with you should you elect to try the drug, I am,

3. Dr. Sharp to Dr. Faget, January 9, 1941:

I am in receipt of the statement of acceptance for Promin, which I interpret as an indication of your desire to investigate the drug in leprosy.

(TRUE COPY)

In Replying, Address The U.S. Marine Hospital

UNITED STATES PUBLIC HEALTH SERVICE

Carville, Louisiana December 9, 1940

Doctor E. A. Sharp Parke Davis and Co. Detroit, Michigan

Dear Doctor Sharp:

I have noted with a great deal of interest the work done at the Mayo Clinic with chemotherapy in experimental tuberculosis in guinea pigs. They seemed to obtain the best results with one of the sulfonamide drugs which was supplied through the courtesy of Parke Davis and Company. The name of this preparation was "Promin".

Will you please inform me if any other experimental work has been done with this drug in acid-fast diseases to determine its value, as well as its relative toxicity? Could a sufficient supply of it be obtained to test its action in leprosy? If so, we would like to try it at the U. S. Marine Hospital, Carville.

Any literature which you can send us on "Promin" would be appreciated.

Yours truly.

(sgd.) G. H. Faget

G. H. Faget, Surgeon Medical Officer in Charge

GHF: ecg

THIS IS A CERTIFIED TRUE COPY

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Notary F. My Commission Expires Dec. 12, 1000

FIG. 1. Certified copy of letter of inquiry about Promin from Dr. G. H. Faget, of Carville, to Dr. E. A. Sharp, of Parke, Davis & Company.

For experimental purposes ampoules in two sizes are being supplied, one containing 2 Gm. of the drug and the other containing 5 Gm. In accordance with my previous letter, the route of choice is intravenous and I would suggest that 2 Gm. daily be given to one series and 5 Gm. daily to another. The contents of each ampoule can be diluted with 5 per cent glucose solution in the amount of 10 to 15 cc. in order to prevent reaction, although untoward phenomena are not anticipated on the basis of our past experience.

Trusting you will keep me advised regarding your requirements, I am [etc.]

(TRUE COPY)

December 18th, 1940

Dr. G. H. Faget, Surgeon Medical Officer in Charge U. S. Marine Hospital Carville, Louisiana

Dear Dr. Faget:

. I have your letter of December 9th referring to the work of Feldman and Hinahaw, of the Mayo Clinic, on diaminodiphenyl sulfone, Promin, in experimental tuberculosis.

The Mayo publication is the only report that has been made although comparable results were obtained in a local institution shortly after general investigation of the drug was initiated about two years ago. Dr. E. V. Cowdry, of Washington University, St. Louis, has made a study of Promin in rat leprosy but to date I do not know the outcome of his observations. I have no doubt that he would be willing to discuss the subject with you.

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Avaiting with interest further developments and assuring of my willingness to cooperate with you should you elect to try the drug, I am, ents

Sincerely yours,

E. A. Sharp, M.D., Director, Dept. Clinical Investigation.

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4. Dr. Faget to Dr. Sharp, January 21, 1941:

We received the drug "Promin" which you recently sent us for experimental purposes, 150 ampoules each of the 2 Gm. and 5 Gm. sizes.

We are having a slight influenza epidemic and therefore will postpone use of the drug for several weeks. If we feel that we are getting satisfactory results from its use, I will probably call upon you to furnish more of the ampoules at a later date.

Thanking you for your cooperation, I am [etc.]

from Dr. E. A. Sharp, replying to the inquiry of Dr. G. H. Faget.

FIG. 2. Certified copy of letter

5. Dr. Faget to Dr. Sharp, April 9, 1941:

We would like to have another supply of Promin to be used in the experimental work we now have under way here, as our supply will be exhausted within two weeks. Thanking you for this and other courtesies, I am [etc.]

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As regards the experimental trial of Promin on murine leprosy mentioned in Sharp's letter to Faget of December 18, 1940, Dr. Cowdry has kindly allowed me to quote the pertinent section from his personal diary of December 28, 1939:

Met Simpson [Dr. Walter M. Simpson of the Kettering Institute, Dayton, Ohio] when he joined my train at Dayton going to Columbus. He suggested that I test action of Promin, expressed much interest in cancer program at Barnard [Hospital, St. Louis] and asked me to explain it to Kettering that afternoon in Columbus.

Dr. Cowdry has kindly provided me with a copy of his letter of December 29, 1940, to Dr. Simpson. I have also obtained, through Dr. Sweet, copies of Dr. Sharp's letter dated January 10, 1940, to Dr. Cowdry offering him a supply of Promin and of Dr. Cowdry's reply of February 16, 1940, acknowledging receipt of ampoules of Promin "in good condition" on that date.

After learning about the rat leprosy experiment, Dr. Faget wrote to Dr. Cowdry. Copies of his letter and of Dr. Cowdry's reply, given to me by Dr. Cowdry, follow:

Dr. Faget to Dr. Cowdry, January 21, 1941:

Through the courtesy of Dr. E. A. Sharp . . . we have secured a supply of 'Promin' for experimental investigation in leprosy.

Dr. Sharp advises me that you have been doing some experimental work with this product in rat leprosy. It will be appreciated if you would inform us what the results have been in your observation in the use of this drug in the treatment of rat leprosy. This information would be of great help to us before we institute our investigation at this hospital.

Dr. Cowdry to Dr. Faget, January 23, 1941:

In answer to your letter of January 21st, I am glad to report as follows regarding our experiments with Promin.

Fifteen rats received subcutaneous injections of Promin daily for 135 days and an equal number were kept as untreated controls. During this period nodules were measured every four days. Enlargement of the nodules was somewhat irregular but it was apparently a little less in the treated than in the control animals. We are now plotting out our results and I shall be able to give more details about changes in size soon. The survival time of the treated animals was longer than that of the untreated ones. Moreover, the treated animals appeared to be in better condition than the others. Their average weight was 66.1 mg. greater. We have never at any time found evidence of harmful action on the part of the Promin.

A full report is being prepared on these experiments as well as on my work on injections of starch and heptaldehyde. A copy will be sent to you. If you require any further information now please let me know. I shall be interested to learn about the experiments you are planning.

The results in murine leprosy, and especially the low toxicity observed in another long-term experiment in a different species from that used in the tuberculosis trial, as well as some indication of suppressive activity, must have encouraged Faget to proceed. The report of the murine leprosy experiment was published by Cowdry and Ruangsiri (¹³) in October 1941.

EARLY EXPERIENCE IN TREATMENT OF LEPROSY WITH PROMIN AND OTHER DISUBSTITUTED SULFONES

Because of the delay caused by the outbreak of influenza, Promin was not administered to patients at Carville until March 1941. A rather curious fact is that, although Dr. Sharp had emphasized in his letters that the route of administration of Promin had been limited to the parenteral, particularly intravenous, route, Faget *et al.* (²¹) decided to try the drug by mouth.

In our preliminary studies Promin was given by mouth to a group of 10 patients. Small doses of $\frac{1}{2}$ to 1 gm, were tolerated for such short periods that therapeutic effects seemed unlikely by this method of administration.

The intravenous route was thereupon adopted. The great majority of patients of the first group received from 1 to 5 gm. daily, 6 days a week. Most of them were given the 5-gm. dose and the treatment was continued for months with intervals of rest of 1 to 2 weeks, 3 times a year. The Promin concentration in the blood showed a rapid decline after a single administration. Only traces remained six to eight hours after the intravenous injection of 5 gm.

Faget *et al.* (²¹) had previously treated a small number of patients with sulfanilamide. Results had not been promising, except in the healing of secondary infections. Toxic manifestations had been frequent and rather severe. They now found that the administration of Promin was not free from toxic reactions, of which the most important was a slow destruction of the erythrocytes. In the majority of cases, however, antianemia therapy, without interruption of Promin treatment, was successful in raising the quantities of red blood cells and hemoglobin to their former levels. After hemolysis, the most important toxic reaction was dermatitis, generally manifested as a diffuse maculopapular eruption accompanied by intense itching. This was observed in 16 per cent of cases. Promin was always discontinued.

In a majority of these allergic patients, desensitization is feasible after the eruption has completely disappeared. Promin is resumed in minute doses, 0.1 gm., intravenously. By gradually increasing the dose over a period of approximately one month, it is possible to arrive at therapeutic doses of 2 gm. daily without further allergic reactions. In some cases full doses of 5 gm. are eventually reached without a recurrence of dermatitis.

In all the patients of the first group treated at Carville the disease was moderately or far advanced when Promin treatment was initiated. Also in all or nearly all of them it was of the lepromatous type, and all patients were bacteriologically positive. Of 22 who had taken at least 12 months of treatment, the disease in 15 was reported as improved, in 6 as stationary, and in 1 as worse. In 5 patients the bacteriologic findings became negative. As regards the value of Promin the authors concluded that this drug

... 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.

Promacetin.—Recognizing that leprosy is subject to more or less prolonged periods of spontaneous remission, Faget et al. (23) undertook a small controlled experiment with this drug. This sulfone was also synthesized at the laboratories of Parke, Davis and Co., and was at first called "Internal Antiseptic 307," and later by the registered name, Promacetin. Chemically, it is sodium-4,4'-diaminodiphenyl-sulfone-2-N-acetylsulfonamide. It was administered orally in capsules to one group of 20 patients, while a placebo (lactose with a trace of quinine), similar in taste and appearance to the active drug, was given to another group of the same size. Presumably all or most of the patients suffered from the lepromatous type and were bacteriologically positive -although definite statements on these points are not made. "The group of patients taking the I.A. 307 and those of the control group were closely matched as to type and stage of the disease." After eight months the course of the disease was checked in a considerable percentage of the treated patients but not in those of the control group. "Complications of the disease such as ulcerations, rhinitis, laryngitis and iridocyclitis frequently improved under I.A. 307 but were unaffected in the control patients." In two of the treated patients the bacteriologic smears became negative, but this did not happen in any of the controls.

A later report on Promacetin in leprosy by Johansen *et al.* (³⁷) was also favorable. A curious feature of Promacetin is that it lacks any effect on experimental tuberculosis in the guinea-pig. It is poorly absorbed and acts as the entire molecule; that is, it does not break down to DDS.

Promizole.—In 1942 Bambas (¹) reported the synthesis of 4,2'diamino-phenyl-5'-thiasole sodium which is registered by Parke, Davis and Co. under the name of Promizole. It proved to be as effective as Promin in experimental tuberculosis in the guinea-pig. It was tried in leprosy at Carville by Faget *et al.* (²²), commencing in March 1943, the maximum dose being 8 gm. daily. Only 11 patients were treated, and in 4 the drug was discontinued—in 2 because of toxicity. The remaining 7 were treated for at least a year. Clinical improvement was observed in 6 cases, but bacteriologically they remained positive. Sharp

and Payne (⁵⁰) remarked that the difficulty of manufacture of Promizole increases the cost to a point which limits its use in therapy.

Diasone.—Diasone is the registered trade mark of the Abbott Laboratories for sulfoxone sodium (disodium formaldehyde sulfoxylate diphenyl sodium) which was synthesized simultaneously and independently in 1937 by Raiziss (⁴⁷) and by Bauer and Rosenthal (²). The first report of its clinical use in leprosy was made in 1944 by Muir (⁴⁵), working in Trinidad. Numerous other favorable reports followed, and the drug attained wide usage after it was made available commercially in 1946.

Sulphetrone.—Another disubstituted compound, tetrasodium 4:4'-di-(3-phenyl-1:3 disulfopropylamino)-diphenyl sulfone, to which Burroughs Wellcome and Co. have given the proprietary name Sulphetrone, was prepared by Gray and Henry in 1936 [Brownlee (⁵)]. Restudy of its properties in 1941 drew attention to its antituberculosis activity. The first report of its use in leprosy was made by Wharton (⁵⁵) in British Guiana. Sulphetrone proved to be very well tolerated in effective dosage and came into extensive use.

Monosubstituted sulfones.—These compounds have not been used widely in leprosy, and none has been subjected to an adequately controlled trial. One of them, succinyl-diaminodiphenyl sulfone (Exosulfonyl of Theraplix, Paris) was reported by Floch and Destombes (³⁰) in 1951 to have given about as good results as DDS in patients treated in French Guiana.

RENEWED INVESTIGATION OF DDS

The first evidence that the toxicity of DDS had probably been exaggerated came from veterinary medicine. In 1941, McEwen *et al.* (⁴³) published the results of preliminary trials of the administration of DDS to normal cattle and to cattle affected with streptococcal mastitis. In comparison with a sulfonamide they found DDS to be effective and to be well tolerated. The initial doses varied from 18 to 180 gm. They continued with one-half the initial dose every 12 hours for 7 days. In the case of the highest dose (180 gm.) only one subsequent dose was given because of signs of damage to the central nervous system. Extremely high blood levels (e.g., 6 mgm/%) were observed in the cattle without any signs of toxicity.

In 1942, Smith *et al.* (⁵¹) reported finding DDS to be much superior to the sulfonamides in action against *M. tuberculosis* in the guinea-pig, both *in vitro* and *in vivo*. Feldman *et al.* (²⁷) stated that DDS was particularly effective in experimental tuberculosis in the guinea-pig on prolonged administration, and that it was well tolerated in doses of about 150 mgm. daily.

FIRST USE OF DDS IN LEPROSY

The first to use DDS in leprosy were Cochrane et al. (11). Learning from Francis (³²) of its use in cattle, they obtained from Imperial Chemical Industries a 25 per cent suspension of DDS in peanut oil. This was given by subcutaneous injection to a small group of patients in a dosage of 5 cc. (1.25 gm. DDS) twice weekly. Severe anemia occurred in several patients, but there was no evidence of hepatitis. At the Vth International Leprosy Congress held at Havana in 1948 (Memoria, p. 272), Cochrane mentioned the use of a 25 per cent suspension of DDS in arachis oil and of a 25 per cent suspension of Sulphetrone with 0.5 per cent beeswax. At Cochrane's suggestion, Molesworth and Narayanaswami (44), working in Malaya, tried a 20 per cent suspension of DDS in coconut oil (0.5% phenol) in 100 cases of lepromatous leprosy. They continued treatment for one year in a dosage of 1 gm. weekly. Clinical improvement was observed in 96 patients, bacteriologic improvement in 27. There were reactions in 71 cases, and 27 had to be treated in the hospital, but the treatment schedule was not interrupted.

Oral use.—Souza Lima (⁵²) in Brazil, Lowe and Smith (⁴¹) in Nigeria, and Floch and Destombes (²⁹) in French Guiana, were the first to try DDS in leprosy by the oral route.⁵

Souza Lima states that his treatment with DDS was initiated in June 1948 in 46 lepromatous cases. The dosage was 0.3 gm. daily. Tolerance was good after an initial anemia, and the early therapeutic results were promising.

In the annual report of the BELRA Research Unit of Nigeria for 1948 (³) there is an account by Lowe of a preliminary trial of six weeks in 9 patients at Uzuakoli. Doses up to 0.5 gm. daily were well tolerated. A blood level of 1 to 2 mgm. per 100 cc. was obtained, and it was maintained with much smaller doses. A group of 54 patients was then placed on a standard dose of 0.3 gm. daily. At the end of six weeks there were no signs of toxicity and it was concluded that oral administration appeared to be safer than the parenteral. Lowe and Smith (⁴¹) do not give the precise dates, but in a later publication Lowe (⁴⁰) states that the first group of 9 patients were given DDS daily by mouth from October

31, 2

⁵Cochrane has stated [THE JOURNAL **27** (1959) 68-72] that "Muir first administered DDS (Dapsone by the oral route. He made a suspension of the powder in water and administered it by drops. Following his work Lowe, in Nigeria, began giving DDS in the form of a tablet." The statement of Muir [THE JOURNAL **19** (1950) 299-308], however, is as follows: "In 1947, Dr. Wevill of Imperial Chemical Industries, Ltd., suggested to the writer that 4:4'diamino-diphenyl sulfone (DDS), the parent substance of the proprietary sulfones, might be worthy of trial. . . As a result of our conversation, Wevill arranged that a supply of DDS should be sent out to Nigeria for experimental use by the staff of the Leprosy Research Unit at Uzu-akoli, under Dr. John Lowe, who chose to administer it orally. The first results obtained there have already been published.

[&]quot;It was not until April 1949 that the writer himself, by then working at the Purulia Leper Home in India, had an opportunity to test this drug. This paper describes certain findings after a year's trial by the oral route."

to December 1948, and that treatment of the larger group was commenced in December 1948.

Under date of April 30, 1949, Floch and Destombes (²⁹) described the use of DDS by the oral route in French Guiana as follows:

En November 1948 nous avons enterpris l'experimentation de ce produit dans la lèpre. Depuis cette date jusqu'a fin Avril 1949, 86 malades ont ete soumis a l'action de la diamino-diphenyl-sulfone tant par voie buccale que par voie intramusculaire.

It is also stated in that report that 64 patients were treated orally and 22 by injection. A dosage of 200 mgm. per day was found to be active and nontoxic.⁶

Bushby (⁷) comments on the delay in the use of DDS in leprosy as follows:

That DDS should have been the first sulphone to possess activity against mycobacteria, and yet was not widely advocated for the treatment of leprosy till its derivatives had been given for almost ten years, makes an interesting object lesson in the difficulties that can arise in the application of a form of treatment for which there is no experimental basis; the fundametal causes of this failure to use DDS earlier were insufficient knowledge of the mode of action of the sulphones and of their fate in the body. In retrospect there also appears to have been a failure to appreciate the need to compare toxicities of drugs not in terms of weight but in therapeutic efficiency, i.e., to compare their therapeutic indices. [He adds that attempts were made to use DDS in man about 1940 for the treatment of streptococcal infections, but] the assumption was made that the dose and concentration attained in the blood should be of the same order as of the sulphonamides, and these doses proved to be too toxic.

The discovery of streptomycin caused an immediate loss of interest in the treatment of tuberculosis with sulfones. This was doubtless a factor in delaying the use of DDS in leprosy. World War II was also responsible in part. Between 1943 and 1946, Promin and other sulfones did not attain extensive usage. It was only when hostilities had ceased, when free communication between scientists was restored, and when supplies of drugs became available that experimental therapy of leprosy became possible on any considerable scale. The most significant early events in promoting the use of sulfones were the Second Panamerican Conference on Leprosy, held in Rio de Janeiro in 1946, and the Fifth International Congress, held in Havana in 1948.

CONTROLLED STUDIES OF CHEMOTHERAPY

In leprosy it is essential that therapeutic trials be adequately con-

⁶In a review by Lowe and Davey in the Transactions of the Royal Society of Medicine and Hygiene **44** (1951) 656 the following note appears:

[&]quot;It now appears that the oral use of D.A.D.P.S. in leprosy originated in 1948 in three different centres, each centre apparently being ignorant of the work of the others. The three centres were, in Nigeria (Lowe and Smith), in Brazil (De Souza Lima), and French Guiana (Floch and Destombes). All three centres in 1949 issued and published accounts of their work. All have used roughly the same daily dose, 100 mg. to 300 mg. All find it safe and clinically effective. Cochrane (1948) was apparently the first to use D.A.D.P.S., but he (Cochrane *et al.*, 1949) gave twice-weekly injections of doses which he reported to be too toxic for wide use, though results were good. Molesworth and Narayanaswami (1949) later used twice-weekly injections of smaller doses with success. In a personal communication, Molesworth states that the main reason for giving injections is psychological; his patients believe in injections of medicines. Our work here was undertaken at the suggestion of Dr. E. Muir."

trolled. The disease has a low mortality, and its natural course may be prolonged over many years with occasional exacerbations and remissions but with a usual tendency towards inactivity and arrest. Bacteriologic changes are difficult to interpret, because natural variations take place in both directions. There is no practical method for distinguishing damaged or dead *M. leprae* from those which are living and multiplying. The skin of an animal takes months to rid itself of killed mycobacteria, and it is therefore probable that in lepromatous leprosy smears would continue to be positive for a long time even if some new and highly bactericidal remedy were discovered.

The first application of the modern techniques of controlled studies in the evaluation of drugs in leprosy was made in 1952 by the Leonard Wood Memorial in cooperation with institutions in the Philippines, Japan, and the Union of South Africa. Generous support for this work was received from the U. S. Public Health Service and from several pharmaceutical manufacturers. These studies have been limited to the lepromatous type of the disease.

In the first series, as reported by Doull (¹⁷), DDS, Diasone and dihydrostreptomycin were shown to be about equal to one another, and superior to a placebo used as a control in Japan and the Philippines, and equal or superior to sodium *p*-aminosalicylate used as a control in South Africa. A combination of Diasone and dihydrostreptomycin gave no better results than either used alone. In the second series, [Doull *et al.* (¹⁸)], supplementation of Diasone or of dihydrostreptomycin with isoniazid gave no better results than were obtained with Diasone alone. In the third series [Doull *et al.* (¹⁹)], no evidence was found that supplementation of DDS therapy either by nicotinamide or by vaccination with BCG gave any advantage over DDS used alone. In the fourth series, recently completed,⁷ a dosage of 2.5 mgm. of DDS per kgm. of body weight was found equal to a 4.0 mgm. dose, and a 4 butoxy-4' dimethylaminodiphenyl thiourea (SU 1906) was found to be little if at all inferior to DDS.

Trials are now under way at two Philippine institutions of an ethyl mercaptan compound (Etisul) manufactured by Imperial Chemical Industries, for which there has been a favorable report by Davey and Hogerzeil (¹⁴). Unfortunately, this drug has two handicaps: it must be given by inunction because a satisfactory preparation for either oral or parenteral use is not available, and it has an odor resembling that of garlic. The experiment is a double blind one, that is, a control group is receiving inunctions with an ointment resembling Etisul but not containing any mercaptan, and neither the physicians nor the patients

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⁷Subsequent to the time this paper was prepared, the results of the fourth series were published by Doull *et al.* (20).

know which is the trial drug. Both groups are receiving DDS as their basic treatment.⁸

Of the disubstituted sulfones only Diasone (Diamidin) has been used in the Memorial's studies. There is, however, accumulating evidence that none of those at present available is superior to DDS. This applies to the compounds previously mentioned and also to newer ones such as diaminodiphenyl sulfoxide which has been used by Buu-Hoi (¹⁰) in Viet Nam, by Davey *et al.* (¹⁵) in Nigeria, and by Laviron *et al.* (³⁸) in French West Africa.

The earliest and most evident improvement observed in patients during sulfone therapy occurs in the ulcerative lepromatous lesions of the skin and mucosa. Nasal obstruction and hoarseness are usually greatly improved within three to six months. Lessening of diffuse infiltration of the skin and disappearance of plaques and nodules takes place much more slowly. The histologic pattern becomes predominantly atrophic, resembling that which occurs in spontaneous remission without treatment of any sort [Fite and Gemar (²⁸)].

From analogy with their in vitro action against M. tuberculosis which is reversed by p-aminobenzoic acid—and from the slowness with which improvement takes place in leprosy, the sulfones may be assumed to have a bacteriostatic rather than a bactericidal effect on M. leprae. This conforms with the fact that bacteriologic negativity, as judged from microscopic examination of smears from the skin, is attained very slowly. After one year of sulfone therapy about 90 per cent of lepromatous patients still have positive smears, and 40 to 50 per cent are still positive after five years of treatment. Smears from the nasal septum improve, but they do not become negative as soon as was formerly thought. Bacteriologic improvement, short of negativity, may occur without specific therapy but is more rapid when sulfones are given. Obviously this improvement may be significant in the control of the disease.

Invasion of nerves probably occurs in every case of leprosy. When localized to the cutaneous nerve supplying a macule or plaque this may be of little consequence, but when the peripheral nerve trunks are invaded the situation is very different. Repeated, extremely painful, and destructive attacks of neuritis may occur—especially of the ulnar and peroneal nerves. By the time many patients seek treatment, serious damage to important nerves has taken place. Extensive anesthesia (often of the glove and stocking distribution), contractures, atrophy of skin and muscles, and some absorption of the bones of the hands and feet may already be present. These changes are irreversible, although surgery and physical medicine can do much to restore function. The

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⁸At the end of 48 weeks the condition of both groups was about the same, clinically and bacteriologically.

basic question as to whether early sulfone therapy can prevent or limit nerve damage remains to be answered.

THE NEED TO FURTHER RESEARCH

The primary handicap in the testing of sulfones and other compounds for therapeutic effectiveness in leprosy is the impossibility of obtaining any clue to their probable effect by direct screening against M. leprae. There is no known method of cultivation of the bacillus, and an animal susceptible to infection has yet to be found. In the meantime, the only alternate is to select for clinical trial those drugs which show activity against other species of the genus Mycobacterium. The path of analogy, although the rational one, has not been smooth. Certain drugs, notably isoniazid, which have been found active against tuberculosis, have been disappointing in leprosy. Nevertheless, let us keep in mind that it was analogy with tuberculosis that led to the discovery of the value of the sulfones in leprosy.

Murine leprosy, caused by *M. leprae murium*, can be readily transmitted to rodents—rats, mice, and Syrian hamsters. This disease has been used in screening and has furnished much valuable information. It would seem quite practicable to extend screening studies and to test all available drugs which have theoretic value not only against experimental tuberculosis and murine leprosy but against a number of other transmissible mycobacterial infections. Among the recently discovered species which have been used only in a very limited way for this purpose are *M. ulcerans* and *M. balnei*, both of which cause ulceration of the skin in man and laboratory animals.

It is important that studies of the pharmacology of the sulfones should be continued, in the hope that more effective compounds of low toxicity may be found. DDS, in vitro, is much more active against M. tuberculosis than any of its derivatives, but there is uncertainty as to the mechanism of its action. From a study of DDS and about sixty of its derivatives Youmans and Doub (54) concluded that maximum in vitro activity against M. tuberculosis is associated with the presence of two free amino groups. If this be true of the substituted compounds, in which one or both of the amino groups are substituted, these groups must become free in vivo, that is, the substituted compound must be partly or completely hydrolyzed in the body. When given orally, many of these compounds, including Promin, break down in the stomach. This explanation, however, does not account for the beneficial action of Promacetin which does not break down to DDS, or for the action of Sulphetrone when given parenterally, or for that of Promin which is always given intravenously.

Relatively recently, evidence has been obtained by Bushby and Woiwod (⁸) that the action of substituted sulfones, and perhaps that of DDS itself, is due in part to the formation of monosubstituted metab-

olites. If this be the case, two free amino groups are not essential. As already mentioned, monosubstituted sulfones have been little used in leprosy and these findings warrant further trials. For valuable discussions of this subject reference is made to correspondence in the International Journal of Leprosy (12) and to Bushby (6).

Chemical, bacteriologic and pharmacologic research is necessary for development of new drugs of stronger antibacterial action than the sulfones possess. With the decline of tuberculosis there has been a lessening of interest in the search for compounds possessing activity against the mycobacteria. The importance of leprosy as a world problem is ample justification for a revival of interest and for governmental support if this be required.

The greatest need in leprosy can be summarized in one sentence: It is for scientists who can combine the knowledge and skill of the modern era with the spirit and determination of their great predecessors, notable among whom was Paul Ehrlich.

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