NEW DEVELOPMENTS IN THE THERAPY OF LEPROSY [1]

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In considering the new developments in the therapy of leprosy one should bear in mind that the therapy of any such disease must always be viewed in the light of its pathology and bacteriology. It must also be realized that, from the point of view of the vast numbers of persons suffering from leprosy in the endemic centers of the world, even an effective remedy which is costly and not within reach of the poor, or which is inconvenient to administer, is of little practical value except as a guide to further research.

It is an accepted fact that *Mycobacterium leprae* is a pathogen of low virulence. The defensive mechanism of the body is seen—in certain cases—in the development of tissue immunity. The successful form of tissue defense, which prevents the multiplication of the organism and leads to spontaneous healing of the disease. Lepromatous leprosy is a progressive disease in which the tissues of the body are unable to organize an effective defense. I believe that without active multiplication of the leprosy bacillus in the corium of the skin it is impossible to develop lepromatous leprosy; and this means that the strategic point of attack against it is in the cutaneous tissues. Hence a drug to be effective must either be injected into the corium, or become concentrated there sufficiently to act on the bacilli at that level.

HYDNOCARPUS THERAPY

Thus it is that advocates of hydnocarpus therapy (i.e., use of the oil and its derivatives) are increasingly insistent on intradermal injections as well as increased dosage. Both Schujman and I laid stress on this point at the International Congress of Leprosy held in Havana last month. Schujman, in recent papers

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(14, 15), has emphasized the view that the success of hydnocarpus therapy depends on dosage and proper administration. He believes that any method of such therapy which does not include intradermal injections, or in which the patient receives less than 400 cc. of the remedy in the year, must be considered inadequate.

I agree with Schujman largely when he blames the failure of hydnocarpus treatment on insufficient dosage and faulty administration. At Havana (1) I presented evidence that with our cases in India, and in spite of our strict bacteriological standards (no case is considered quiescent unless all of 16 skin smears are negative, the examination repeated monthly for 6 months), by intensive intradermal plus subcutaneous injections of hydnocarpus oil, in a dosage of 15 cc. per week, 50 per cent of the early lepromatous ones become negative in less than two years.

The Committee on Therapy of the Havana Congress (11) did not recommend discarding altogether the hydnocarpus preparations, but pointed out that they should be given in adequate doses (15-25 cc. or more per week), with intensive intradermal medication. It must be admitted, however, that the advocates of hydnocarpus drugs have not been altogether satisfied. They have viewed with considerable uneasiness the high rate of relapse after recovery, and the relative lack of success in advanced lepromatous leprosy is most disappointing. This form of leprosy therapy is much less effective in European and Mongolian racial groups than in Indians and Africans. The modern advance represented by sulphone therapy is, therefore, greatly welcomed. In discussing these new remedies, however, a sense of perspective must be maintained lest there be a repetition of the uncritical enthusiasm of 25 years ago when the hydnocarpus derivatives were rediscovered. If that occurs, these new drugs may be discredited and progress indefinitely retarded.

SULPHONE THERAPY

The parent substance of all the sulphone derivatives, diaminodiphenyl sulphone, has been known for many years but until recently has been considered too toxic for human use. In 1940 Feldman, Hinshaw and Moses (9) first reported on the use of the derivative called promin in the treatment of experimental tuberculosis. In 1943 and subsequently, Faget *et al.* (7, 4, 8,) reported that it showed definite effect in lepromatous leprosy. In 1944-1946, Muir (13), Faget *et al.* (3, 6) and Fernandez and

Carboni (10) reported on the use of another derivative, diasone; in 1946, Faget *et al.* (5), and later Johansen and Erickson (12), reported on a third one, promizole; and in 1947, Wharton (16) reported on a fourth one, sulphetrone, claiming that it was less toxic and more effective than either promin or diasone.

In this presentation I shall discuss briefly the experimental work with the sulphones which we have done in Madras during the past two and one-half years, and then pass on to what may be important further developments in the administration of these drugs. Promin was first used in our experiments, then diasone, and finally sulphetrone was included. A recent review of our results has led to the conclusion that, with little doubt, the diaminodiphenyl sulphone derivatives are effective in lepromatous leprosy in that they cause marked clinical improvement of the lesions, but that the bacteriologic improvement is not commensurate and is much slower.

Promin (*diaminodiphenyl sulphone dextrose sodium sulphonate*).—This substance appears to be unsuitable for routine use in Indian patients. All our cases put on this drug requested that it be discontinued because of weakness and, in two cases, progressive anemia. At Carville, however, the majority of patients are on promin.

Diasone (*diaminodiphenyl sulphone formaldehyde sulphonate*).—A majority of our cases showed significant clinical improvement, but in 8 out of 30 the clinical condition was either stationary or worse. The bacteriologic condition showed no improvement or had deteriorated in 12 out of 30, and no case had become bacteriologically negative in the average of nineteen months—admittedly too short a period for definite conclusions to be drawn. With the dosages given there was a marked tendency (13 cases out of the 30) for the drug to precipitate lepra reaction with erythema nodosum-like lesions. Usually these reactions subsided when treatment was continued, in 4 cases the condition was severe, and 3 had to discontinue diasone because of its persistence.

Sulphetrone (*diaminodiphenyl sulphone phenylpropylaminotetrasodium sulphonate*).—We agree with Wharton that sulphetrone appears to be more rapid in action and less liable to produce lepra reaction than any other sulphone now in general use. In only one out of nine cases was there reaction of sufficient severity to necessitate the discontinuance of treatment. In an average period of thirteen months, 8 cases were much improved clinically and bacteriologically, while in 1 the bacteriological

status deteriorated and the clinical condition remained stationary. The dosages of sulphetrone were considerably greater than those of diasone—500-700 grams of diasone compared with 1,500 to 2,400 grams of sulphetrone in the periods stated. Therefore, apart from the inconvenience of taking large doses, sulphetrone appears to be, at present, the sulphone derivative of choice.

Other drugs used recently.—Promizole is a sulphone derivative which has been tried at Carville, as mentioned, but it was given up because it is not superior to diasone or promin, and it is too costly to justify manufacture. Streptomycin has also been tried out there (2) to be discontinued; not only does it appear to be ineffective, but its toxicity in the dosages used makes it impracticable.

In the sulphones we have new and powerful remedies for advanced and moderately advanced lepromatous leprosy, but in India early lepromatous cases have not responded to them as rapidly as they have to adequate hydnocarpus therapy. For the present, therefore, we reserve sulphone therapy for the more advanced lepromatous cases, for those cases which have not responded to hydnocarpus therapy or which have relapsed, and for lepromatous cases among the European, part-European and Mongolian racial groups. It must, however, not be forgotten that while there is considerable improvement in the majority of advanced lepromatous cases after a year's treatment, and frequently dramatic improvement, bacteriologic improvement is much slower. It is still a question whether a significant number of advanced lepromatous cases become bacteriologically negative even after 3 or 4 years.

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 (Wolcott, 17). 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.

In the case of diasone an initial dose of 0.9 gram (3 tablets) per day is given; this is increased by 1 tablet per day each month until a maximum of 6 tablets per day is reached. In the case of sulphetrone, our commencing dose is 4 tablets a day, increasing every second day by 2 tablets until a maximum of 12 per day is reached.

Because lepra reaction, particularly of the erythema nodosum type, is generally seen at the lower dose levels; because reactions frequently subside despite the continuance of sulphone therapy; and because children can tolerate adult doses of diasone with no increase in the incidence of reaction, it is my opinion that these drugs should be maintained at their maximum dosages for prolonged periods—a year or more—without rest intervals unless there are signs of intolerance. These signs are: (*a*) hematuria, of which we have not seen a case; (*b*) progressive anemia, which responds rapidly to full doses of iron and vitamin B complex; (*c*) persistent lepra reaction.

Although it can be fairly claimed that the sulphone preparations hold out an almost sure hope of amelioration of the advanced lepromatous case, with the definite possibility of complete relief of the distressing complications associated with lesions of the nose and throat, the present methods of administration have certain real disadvantages. (1) Oral administration is unsatisfactory because the exact amount of the drug absorbed cannot be estimated, the inconvenience of swallowing a large number of tablets per day is not inconsiderable, and in the case of ignorant people, or large masses, adequate supervision is well nigh impossible. (2) Intravenous administration has equally serious disadvantages because it needs trained personnel not readily available in India and the East; and it usually results in rapid absorption but equally rapid excretion.

It is surely logical to expect that a drug for leprosy treatment should be sold at a reasonable price, and should be possible of administration in a practical but economical way. Oral administration is extravagant, intravenous medication costly.

EXPERIMENTAL INVESTIGATIONS

For the reasons just given, we have sought alternative methods of administration. Because we believe that the corium of the skin is a strategic point of the attack against the infection, it has been given an important place in this work.

Intradermal injection.—The first modification tried was intradermal injection. For that we used the parent substance (diaminodiphenyl sulphone, or "DDS"), in a suspension 15 per cent in arachis oil. To test the efficacy of this method we undertook estimations of the concentration of substance in the skin, the results expressed in milligrammes per gramme of tissue. For comparison, determinations were made of the skin of the area given the intradermal injections and of skin from the

opposite side, which had not been injected. The experiment was repeated several times. The concentration in the control area was found to be as high as in the injected one, and in some cases higher.

In this work it was found that significant concentrations occurred when either diasone or sulphetrone was given by the oral route. It was therefore concluded that the sulphone derivatives are actually deposited in the skin from the blood stream; and there were indications that they are concentrated there. The intradermal injection method was, therefore, abandoned.

Subcutaneous injection.—Another therapeutic experiment was started in which a 25 per cent suspension of diaminodiphenyl sulphone in arachis oil was given by subcutaneous injection. Later, when the drug became available, we also used a 25 per cent emulsion of sulphetrone with 0.5 per cent beeswax in arachis oil. The preferred dosage of DDS in oil was 5 cc. twice a week. In only two instances did we exceed these dosages, increasing the former to 7 cc. twice a week, and the latter to 7 cc. three times a week. By thus increasing the dose of sulphetrone a severe attack of leprous iritis was aborted, and lepra fever subsided.

We are well aware of the dangers of using DDS suspensions, and until more work is done we are not ready to recommend extensive trials of that substance. The dosage used, however, appears to be well within the limits of tolerance. In no case did the blood concentrations rise above 2 milligrammes per cent. These preliminary results provide evidence, not only that this substance is effective, but that it is more rapidly so than are the derivatives, and that a very much smaller dose of it is required for equivalent and in some cases more marked clinical and bacteriologic results (70 gm. of diaminodiphenyl sulphone against 2,470 gm. of sulphetrone, and 700 gm. of diasone). The average time required with the DDS was 11 months as compared to 16 months with sulphetrone. We have reason to believe that the sulphetrone emulsion will give results equivalent to those obtained when the drug is administered by mouth with much less danger of toxic complications. It therefore seems appropriate that this line of sulphone therapy should be further investigated. If our findings are confirmed some of the disadvantages of the present methods will be eliminated.

Regarding the tendency of the sulphone drugs to precipitate lepra reaction in the early months of treatment, a distressing complication which is sometimes so severe that this therapy has

to be abandoned, recent work by Wharton and the Carville workers indicates that it may be controlled by certain antihistamine drugs; and a couple of reports presented at or to the Havana Congress indicate that streptomycin may be of value in reaction. To be able to control reactions would be of the greatest importance, for it would make sulphone therapy possible for the most active lepromatous cases.

Another development of therapy in leprosy is the increasing attention given to the possible additive, or even synergistic, effects of a combination of remedies. While streptomycin has been discarded for prolonged use in leprosy, it may be found useful in smaller doses and for shorter periods as during the rest periods in sulphone therapy. It is known that experiments are under way (Feldman) with combination sulphone-chaulmoogra therapy in experimental tuberculosis. Suspensions of sulphones in hydnocarpus oil may be the combination of choice. As yet we have avoided using any such preparation because of the obvious criticism which would be levelled at initial experiments made with combinations of drugs.

Mention must also be made of current trials of the substance called rongalite, or formaldehyde sodium bisulphite, which is the substance added to the parent radical to make diasone. According to Carville workers it appears to have the greatest tendency to precipitate lepra reaction of the erythema nodosum type, and it may therefore prove valuable if such reactions can be controlled.

It is evident that the advances in chemotherapeutic and antibiotic substances hold out great promise that, at long last, the therapeutic conquest of lepromatous leprosy may be within sight. In viewing the situation, however, excessive optimism must be resisted. The leprologist is urged not to discard the hydnocarpus remedies, but to use them properly while continuing the search for other and more effective agents, ever bearing in mind that no remedy will be of ultimate avail if it is not practical of administration and reasonable in price.

In concluding this paper, I wish to express regret that the advances in the modern treatment of leprosy have almost entirely been confined to the search for specific remedies. The need for investigations into the application of modern orthopedic, physiotherapeutic, and manipulative measures has been almost entirely overlooked; and the importance of preventing or relieving the distressing sequelae has not been sufficiently stressed. To cure leprosy and leave the patients physical and mental wrecks, the

subjects of ostracism, a drag on society and a misery to themselves, is no credit to us or to the society in which we live.

[The author speaks of this paper as "a little out of date" in that, for routine work, he has definitely given up oral administration of the sulfones in favor of injections of the 50 per cent aqueous solution of sulphetrone. Nevertheless, he is of the opinion that the DDS substance is the most effective remedy in leprosy, but that further experimentation is required before it can be adopted for routine use.—EDITOR.]

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ABSTRACT OF DISCUSSION OF PAPERS OF DRS. JOHANSEN AND COCHRANE

DR. N. R. SLOAN (*Hawaii*): At Kalaupapa we have used sulfones for about two years, and I agree with all that has been said about their value. Ulcers of years' standing clear up within several months; visual failure is arrested; and tracheal tubes are removed. We used to do 8 to 15 tracheotomies a year, but our last one was done a year ago. The patients themselves are enthusiastic. In the last year four children, 6 to 14 years of age, have been brought in by relatives on the occurrence of the first symptoms because treatment is wanted. I thoroughly agree with Dr. Cochrane regarding the need for greater social consciousness. The newspapers are no longer hesitant to mention the word leprosy. As one of our colleagues has said: "This is indeed the new day. I am happy to have lived to see it."

DR. H. W. WADE (*United States*): The present situation in the therapy of leprosy is unparalleled in that no one who has employed the sulfones has rendered an unfavorable report. At every center visited in a recent tour of South America there was nothing less than enthusiasm, on the part of both patients and physicians. Much emphasis was laid on the rapid amelioration of lesions of the mucous membrane of the nose and throat; also the healing of cutaneous ulcers, it being said in some places that the saving in dressings compensated for the cost of the drugs.

Dr. Johansen has summarized well the experience at Carville, which began about 7 years ago. Dr. Lauro de Souza Lima, of the Padre Bento

leprosarium in São Paulo, Brazil, is second as regards time and first as regards numbers of patients treated—a total of 1,287 since 4½ years ago. According to his report at the Havana Congress, in no case under treatment had the disease progressed; less than 4 per cent of 841 lepromatous cases had failed to improve in some degree, and in 23 per cent the lesions had cleared up (in 66% of 99 "incipient" cases). He pointed out, however, that not a few cases improve only to a certain point and then become stationary. Also that bacteriological improvement does not parallel the clinical improvement. In 50 per cent of 150 biopsy specimens from the sites of subsided lesions, bacilli were still to be found, although more or less greatly modified in appearance. This whole experience would seem, in general, to parallel that of the Carville workers.

Remarkable as is the benefit from sulfone treatment, no serious investigator believes that the desired end in medication has been reached. More rapidly acting drugs are needed, or drugs of higher ultimate effectiveness, or more effective methods of treatment. Attention is being turned to the possibilities of combined use of different drugs; certain workers are using, among other things, combinations of sulfones, and a few of them are combining chaulmoogra and a sulfone.

From the practical aspect the present situation arouses some apprehension on the part of those who cannot employ the new drugs for routine mass treatment, but have to rely upon the old chaulmoogra (hydnocarpus) preparations—and see real value in them, when properly employed. It would be most unfortunate if the propaganda for the new drugs in medical and lay publications should serve to discourage the patients where chaulmoogra must still be relied upon.

DR. M. SUCH (*Spain*): During the last two years we have treated 52 patients with sulfones, and the results have been excellent. I should like to stress also the social aspect of leprosy. With the more effective therapy now available, I recommend a propaganda campaign so that patients will seek medical advice. The cost of the sulfones is still high, and I should like to ask this meeting to suggest to the International Leprosy Association that an international formula be reached so there will be uniform price throughout the world.

DR. R. G. COCHRANE (*India*): Dr. Johansen and the other speakers who have given almost unqualified support to sulfone therapy have been working under conditions which have not been favorable to the administration of chaulmoogra oil. The majority of cases which these workers have treated are advanced lepromatous. That is evidently so of the cases treated by Dr. Sloan, from his reference to the necessity of tracheotomy. I believe that no one disputes the supremacy of the sulfones in such cases. To judge the effectiveness of a remedy by the enthusiasm of the patients is deceptive, because whenever good results are reported patients who have suffered for years from a chronic disease are liable to lose their sense of balance. Nevertheless, while one would use the sulfones wherever possible, care must be taken not to overpublicize the results, for in India and the East that would create a demand which would be almost impossible to meet. Such propaganda, therefore, is liable to do more harm than good and to recoil on governments which are unable to meet the demand for these drugs. Further, to base prevention on treatment is unsound; treatment may be a valuable adjunct to prevention, but the keynote must always

be the prevention of contact of open cases with healthy persons, particularly children.

I am particularly glad that Dr. Johansen has stressed the increasing opportunities for and value of plastic surgery following improvement with the sulfone drugs.

I accept Dr. Wade's remark about [Dr. Lauro Souza Lima's observation of] change of tissue reaction from lepromatous to tuberculoid with reservation. Personally I should not be willing, in as important a matter as this, to accept the clinical history that a case had been previously lepromatous without seeing a section from the case. For example, we recently had a case which apparently became negative within three months on sulfone therapy. As this result was too good to be true, I looked up the clinical record and photograph. From both it appeared as if the case were lepromatous. The section, however, showed the histologic picture of atypical leproma, and the diagnosis was atypical or border-line lesion. This I think is sufficient warning that, in regard to our own work, no matter how experienced we are we should maintain a friendly but healthy skeptical attitude.