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STUDIES ON THE THERAPY OF LEPROSY [1]

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Of a score or more experimental treatments employed in human leprosy at Carville only two, chaulmoogra oil and the sulfone drugs, have proved worthy of more than passing consideration. Chaulmoogra oil, of course, had been an established treatment in leprosy long before its use in this country. It was considered experimental only in the sense that it had not had an extensive and critical clinical trial in this country prior to its use at Carville. The sulfones, promin, diasone, and promizole, on the other hand, were first used in the treatment of leprosy at the National Leprosarium. They are now gradually becoming recognized in other countries as efficient therapeutic agents against this disease (1). At the Fifth International Leprosy Congress, held in Habana, Cuba, in April 1948, it was the opinion of the majority of the members of the congress that sulfone must be regarded the treatment of choice (2). Another treatment, streptomycin, which is showing some promise as a therapeutic agent against leprosy, must still be considered to be in the experimental stage.

CHAULMOOGRA OIL

The experience with chaulmoogra oil might best be summarized by quotation of impressions entertained by Denney, Hasseltine, and Faget. These investigators in succession served in charge of activities at Carville and collectively represent a large experience with the drug. Denney (3) in 1926 wrote as follows: "Treatment with chaulmoogra oil is being continued in a large

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group of patients, and while no spectacular results have been obtained either with the oral administration of the crude oil or the intramuscular injections of its ethyl esters, it appears that definite improvement has followed in a sufficiently large percentage of cases to encourage the patients in the continuation of the treatment." Hasseltine (4) in 1938 stated: "A general survey of all patients taking treatment shows a satisfactory amount of improvement, although a considerable number of the older advanced cases show retrogression." Faget (5) in 1942, reporting on his experience prior to the introduction of the sulfones in the treatment of leprosy, said: "Although there was no further evidence of definite specific action, the impression persists that the chaulmoogra oil products are of some benefit in leprosy." In 1946, after the experimental use of the sulfones for a period of 5 years side by side with the routine use of chaulmoogra oil in maximum tolerated doses as reported by Johansen (6), Faget (7) commented as follows: "A smaller number of patients than usual were taking chaulmoogra oil treatments either by mouth or by intramuscular injection. Since chaulmoogra oil and its derivatives have not proved to be specifics for leprosy, their popularity is declining. The impression, however, persists that chaulmoogra oil products are of some benefit in certain types of the disease and so they continue to be used in those cases."

In 1947 chaulmoogra oil was entirely abandoned in favor of the sulfones for the routine treatment of all types of cases of leprosy at Carville. Such a change became inevitable when the comparative results from chaulmoogra oil and sulfones over long periods of time were analyzed. Such a marked superior therapeutic action on the part of the sulfones was demonstrated, in early as well as far advanced cases of lepromatous leprosy, that chaulmoogra oil no longer seemed to have a place as a routine treatment for this type of the disease. Since lepromatous leprosy constitutes approximately 85 per cent of the patient population at Carville and the remaining 15 per cent either respond as well without treatment as with treatment or do as well with sulfones as with chaulmoogra oil, a change in routine treatment was indicated, and accomplished. Chaulmoogra oil, it appears, enjoyed a long period of popularity mainly because of the lack of more efficient drugs. McCoy (8) in 1942 was more or less of the opinion when he concluded from his observations that "the oil and its derivatives are of little or no value" in leprosy.

It must not be inferred from this change of policy in treating leprosy that chaulmoogra oil is no longer considered to be of

any value. It does not appear, however, that its use will be revived to any extent at Carville unless it might be found that a combination of chaulmoogra oil and the sulfones is more effective than either one alone. Also leprologists who report the greatest success with chaulmoogra oil advocate intracutaneous administration of the drug. Since this method of administering the oil proved to be impractical in the Carville group of patients because of the tedious nature of the procedure, the associated pain, and the extensive skin involvement usually present, it might be that recent advances in injection technique, such as the hypospray (9), might make intracutaneous treatment with chaulmoogra oil feasible.

SULFONE DRUGS

The use of promin, diasone, and promizole in the treatment of leprosy has been quite extensively reported in the world medical literature. When first reported (10) promin was regarded to be therapeutically more effective in leprosy than any treatment previously tried at Carville. This opinion still prevails not only for promin but for diasone and promizole as well.

Promin, diasone, and promizole are all derivatives of diamino diphenyl sulfone. It appears, but it is not definitely established, that diamino diphenyl sulfone, the chemical group common to all these drugs, is the active principle.

Promizole is synthesized with much difficulty (11), and because of this fact and because it shows no therapeutic superiority over the other sulfones in leprosy (12), its use may not be extended beyond present commitments, and further discussion of this drug will not be attempted here.

Rapid or spectacular cures are not seen from the use of sulfone drugs nor are they claimed to be specific remedies. On the contrary, they work slowly. Definite objective clinical improvement does not appear until after 3 to 6 months of treatment. As a rule this is first noticeable in mucous membrane lesions; then in skin lesions; followed by an exceedingly slow reduction of *M. leprae* in these lesions as demonstrated in skin and mucous membrane smears. Improvement in these features of the disease are progressive, with few if any relapses. Evidence has also accumulated over a period of years that bone lesions presumably due to the direct action of *M. leprae* heal faster under sulfone therapy than would be expected from spontaneous healing and that a restraining influence is exerted on bone absorption and the further progression of neural lesions (15). The most remarkable or unusual feature, however, to those

who are acquainted with the unfavorable progression of the disease in many cases under chaulmoogra oil treatment, is the almost universal improvement seen under the sulfones and the fact that the disease seldom, if ever, appears to become worse.

From toxicity studies and blood and urine sulfone level determininations, when correlated with therapeutic effects obtained, it has been found that a daily dose of 5.0 grams intravenously in the case of promin and 1.0 gram orally in the case of diasone consistently gives good results. In general, the rapidity of objective clinical improvement is in direct proportion to the intensity of treatment, large doses producing faster regression of nodules, infiltrations and ulcerations than low doses. Individual variation to this rule, however, has been quite frequent, and good clinical response has been observed in many cases on doses as low as 1.0 to 2.5 grams for promin and 0.6 gram for diasone daily. On the other hand, disappearance of *M. leprae* from leprous lesions does not seem to be appreciably accelerated by large doses of the drugs. This has been demonstrated in a group of 10 patients treated intensively with doses ranging from 7.5 to 15 grams of promin daily, given in 3 divided doses at regular intervals. Quantitative bacterioscopic examinations conducted on these patients do not indicate that the number of bacilli have decreased appreciably more rapidly than in those patients receiving only 2.5 to 5.0 grams of promin once daily, although the clinical improvement had been accelerated by as much as 2 months. This may be clearer to our understanding when it is recalled that human leprosy bacilli killed by boiling and injected into rats can still be found 18 months later retaining their acid-fastness. It is possible that dead bacilli may remain identified in the skin for several years following recession of specific leprous lesions from treatment.

Rest periods from drug administration are observed every third week in the case of promin and for a period of 2 weeks every 2 months in the case of diasone. Although it might be expected that drug sensitivity would be produced by such a routine, this has not been our experience. Blood and urine sulfone level determinations have proved that rest periods are not only desirable but necessary to avoid toxic manifestations.

Unusually high concentrations of promin in the blood and urine have been found in several patients 9 days following the last dose of the drug, and one patient who had taken the drug for 6 years had a urine concentration of 0.7 milligram per cent after an enforced rest period of 4 weeks during which time no sulfone

or sulfa drug had been administered (14). It has been shown in the case of sulphetrone, a related sulfone, that greater concentrations of the drug were encountered in the skin in some cases than in the blood stream (15). It can be assumed from this observation that other sulfones as well, such as promin, diasone and promizole, are stored in the skin, and it is possible also that the liver acts as a storage reservoir. Rest periods presumably allow the release of sulfones from storage depots before critical levels are reached.

Another essential feature in the proper administration of the sulfones is to initiate treatment with comparatively small doses. The initial dose of promin should usually not exceed 1 gram and that for diasone 0.3 gram. A period of 2 to 4 weeks should elapse before the maximum dose is attained. Initiating treatment with maximum doses is apt to produce toxic reactions, especially febrile episodes in the case of promin and gastric irritation and hematuria in the case of diasone. In fact, febrile reactions to an initial dose of 1 gram of promin have occurred in some of our patients. These occurrences were undoubtedly sensitivity reactions to promin and not lepra fever. All of these patients when desensitized with small doses (0.01 to 0.1 gram) have been able to reach and be maintained on maximum doses of the drug. Another group of patients when initiated on full doses of diasone developed hematuria without crystalluria. This has not occurred after initial doses were kept low. Also, a large number of patients are apt to develop gastric intolerance if initiated on maximum doses of diasone before tolerance to the drug has been developed.

It has been argued that *M. leprae* is apt to develop resistance against the sulfones if treatment is not initiated with maximum doses and such dosage maintained. This is a possibility more apparent than real and one which must be spoken of mainly by speculation since one is unable to cultivate *M. leprae* artificially in order to determine its resistance to drugs. One group of intensively treated patients who were initiated on maximum doses of promin as routinely given with the doses later increased three-fold have shown no more improvement bacterioscopically than those on routine dosage. Furthermore, during rest periods, sulfones released from storage depots presumably make treatment continuous in spite of rest periods and thus deter development of resistance of the organism against these drugs.

Red and white blood counts and urinalyses have been performed on our patients at regular 3-week intervals. This has

been essential because of toxicity studies. Very rarely, except for the appearance of a low grade anemia which responds to iron therapy, have any abnormalities in these tests occurred since an established routine has been followed. These laboratory tests can possibly be eliminated, except perhaps during the first month of treatment, provided iron therapy is given routinely.

Rest periods and proper initial dosages, it is felt, have materially contributed to the low toxicity record experienced at Carville from the use of sulfone drugs. When it is considered that a number of our patients have taken as much as 10 pounds of promin over a period of 6 years without a single toxic reaction except a low grade anemia, the apparent innocuousness of these drugs when properly administered can be readily appreciated. Unlikely as they are to produce toxic effects, they should not be abused by pushing dosage to the limit. Good therapeutic results have been observed on comparatively small doses. This suggests that minimal effective dose determinations should be ascertained where cost of drugs is of paramount importance.

The mode of action of the sulfone drugs is not definitely known. It has been felt that the diamino diphenyl sulfone radical is the active principle which produces a bacteriostatic action upon *M. lepra*. Another belief is that these drugs depress the red blood cell count sufficiently to produce an anoxia in the tissues which in turn reduces growth of *M. lepra*. This theory is hardly tenable since improvement also takes place in those patients in whom blood counts are kept normal with iron therapy. The slow disappearance of the organism from leprous lesions, however, would indicate that sulfones have little if any direct destructive effect upon the acid-fast organism in the tissue cells. Fite (16) in his study of the histopathology of lesions before and after promin treatment found that promin appears capable of eliminating bacillary infection from the blood stream and small blood vessels. New lesions are thereby prevented from being formed. The lesions already present are then afforded a better opportunity to recede much as they would recede during spontaneous regression.

STREPTOMYCIN

After it appeared likely that streptomycin exerted antibacterial activity against *Mycobacterium tuberculosis* (17) and when the studies of Feldman and Hinshaw (18) demonstrated that this drug exerted suppressive effect on experimental tuberculosis in the guinea pig, a study of what value streptomycin

might have in clinical leprosy was undertaken by Faget et al. (19).

Ten cases of lepromatous leprosy were subjected to intramuscular injections of 2 grams of streptomycin daily in eight divided doses for a period of 4 months, after which the dosage was reduced to 1 gram daily given in two divided doses. Three cases were treated continuously for 11 months, two cases for 8 months and three cases for 7 months; two cases had treatment intermittently at first, because of sensitivity to the drug, after which one was able to continue with full doses for 11 months, the other tolerated only 0.5 to 1 gram daily for 6 months. In addition to streptomycin, five of these patients received sulfone treatment, four promin and one diasone. The four who received promin had previously been on that drug for several months to 2½ years and had failed to register as rapid or as extensive improvement as is usual with the sulfones in that length of time. Of the remainder, four had had no previous antileprotic treatment of any kind and two had had chaulmoogra oil.

Photographically and by clinical examination, changes on the improvement side appeared in the nodular and macular lesions of seven of the patients under treatment, two remained stationary, and one became slightly worse. Nasal observation and epistaxis were checked in a few cases and healing of a leprous ulcer of the soft palate occurred rather rapidly in one patient. The improvement that did occur all happened during the first 2 or 3 months of treatment. After this the condition of the patients remained stationary and that of one became worse. It cannot be definitely said that the improvement noted was more rapid in those patients who were also taking sulfones, although none of these patients became worse during treatment.

The most rapid improvement occurred in mucous membrane lesions. This was later noted in one other patient given streptomycin for scabbing lesions of the mucous membrane of the nose which had been causing obstruction to breathing and epistaxis over a period of years. Partial relief was sustained after 3 weeks on a dose of 1 gram streptomycin intramuscularly daily. The acute symptoms of pain and redness associated with leprous iritis and iridocyclitis has also been observed to be relieved rapidly in several patients to whom streptomycin has been given for these symptoms.

Toxic effects on a daily dose of 2 grams were severe and frequent. Vertigo and eosinophilia occurred in all patients; malaise and fever, headache, flushing of the skin, and skin

eruptions were troublesome in many; and tinnitus and permanent impaired hearing occurred in one patient. Four of these patients still complain of vertigo, especially in going from a light to a dark place, 11, 14, 14, and 15 months respectively after discontinuation of streptomycin. Eosinophilia was usually intense, varying from a low of 5 per cent to individual heights of 42, 43, 47, 54, and 65 per cent, commencing within the first 2 weeks of treatment and progressively increasing to a peak in the twelfth week to 3,400 cells per cubic milliliter of blood. Slowly declining during the next 4 weeks to 1,200 cells, it became stationary until 2 weeks after reducing the dose by one-half; then it declined again. Following discontinuation of treatment, eosinophile counts returned to normal in from 1 to 2 months in five patients. They remained elevated for 6 months in three patients, for 10 months in one patient, and in the remaining patient the count is still elevated (13 per cent) 15 months after discontinuation of treatment. All patients had normal eosinophile counts prior to treatment. Eosinophilia was considered to be a sensitivity phenomenon, but it might be of interest to speculate on the possibility of its being a sign of liberation of firmly bound bacterial lipids and therefore a sign of healing.

Streptomycin, in large and continuous doses produce toxic manifestations too severe in comparison with results obtained. Unless this disadvantage can be overcome, streptomycin must be classed as of doubtful value for systemic use in leprosy. In low concentrations it has been found to be of value when used locally as a solution or in a water soluble ointment base on leprous and tropic ulcerations (20). Local irritation may occur in retreated cases unless low concentrations are employed.

DISCUSSION

The improved status in which the patients at Carville find themselves today as compared to their lot during the height of the chaulmoogra oil regime is mute testimony in favor of the superiority of the sulfones over chaulmoogra oil in the treatment of leprosy. Improvement has been universal whether the patient has been of European, American, or Oriental extraction. Sufficient saving has been accomplished in the decreased need for bandages and materials for the proper care of ulcers to cover the cost of the new drugs employed. Only one tracheotomy has been performed during the sulfone regime, and this was on a patient as yet not treated with sulfone. Tracheotomy during the chaulmoogra oil days was a rather frequent procedure.

Sulfone therapy in leprosy is opening up avenues of treat-

ment that, perhaps, the most radical minded physician and surgeon would never have thought possible during the chaulmoogra oil regime. Correction of facial deformities or disfigurement by means of plastic surgery are entirely successful and feasible procedures in sulfone-treated patients even if the skin shows organisms. Healing of skin incisions is rapid, and scarring or tissue contraction is no more evident than in normal skin. Correction of nasal deformities, grafting of eyebrows, where they were formerly absent, and erasure of cicatricial and redundant distortions of the face are the most common reconstructions attempted.

During chaulmoogra oil days results from orthopedic and physiotherapeutic measures were invariably disastrous. Improvements secured would subsequently succumb to further progression or relapse of the disease. Interest has been revived in such procedures for the relief and prevention of deformities since such measures, it appears, will be more successful under sulfone therapy. The real goal of sulfone therapy, however, is not only to make possible correction of physical deformities but to prevent such deformities by means of early treatment supported by whatever corrective measures are at the doctor's disposal.

It is felt without equivocation that the sulfones must be regarded the treatment of choice at present for leprosy in this country. These drugs, however, are not the complete answer to the treatment problem in leprosy. Further search should be made for quicker acting therapeutic agents. Antibiotics having a demonstrable bacteriostatic effect on acid-fast organisms warrant further investigation, as do new and related drugs of the sulfone series.

CONCLUSIONS

Sulfone drugs have been found to be an effective treatment for leprosy. Their therapeutic action is considered to be superior to chaulmoogra oil and its derivatives, administered in maximum tolerated doses intramuscularly and orally.

Intracutaneous administration of chaulmoogra oil proved impractical in the Carville group of patients. New injection technique such as is possible with the hypospray might make this method of administration feasible.

To secure the best therapeutic results with a minimum of toxic effect, sulfone treatment should be initiated with small doses which are gradually increased as tolerance is developed, and rest periods should be observed.

Increased cost of the sulfone drugs over chaulmoogra oil is largely mitigated by their reducing or making unnecessary expenditure for the care of complications associated with the disease. Determination of minimal effective doses is of value where cost of drugs is of paramount importance.

Streptomycin and other antibiotics having a demonstrable bacteriostatic effect on acid-fast organisms warrant further trial in leprosy as do new and related drugs of the sulfone series.

Although not considered specific remedies, sulfone drugs must be regarded the treatment of choice for leprosy at present.

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[The discussion of this paper follows that of Dr. R. G. Cochrane, p. 291.]