CHEMOTHERAPY IN LEPROSY

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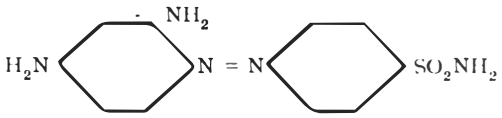
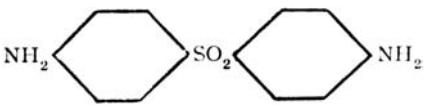
The discovery of the antibacterial properties of the sulphonamides by Domagk in 1935 initiated a new era in chemotherapy and revived an interest in this subject. As a result of the discovery

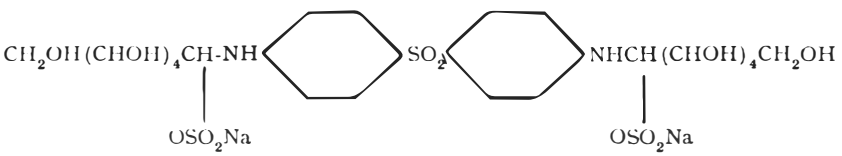


that the activity of ' prontosil ' resides in the sulphonamide anion, it was realized that compounds of allied structures might show similar bacteriostatic properties.

Buttle *et al.* (1937) turned their attention to diaminodiphenylsulphone which was first synthesized many years previously by Fromm and Wittmann

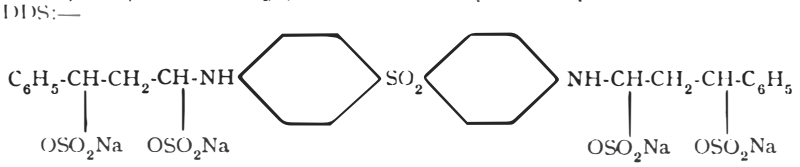


(1908). This substance was found to be very much more effective than the sulphonamides, but experimental work showed that it possessed a high degree of toxicity. Feldman *et al.* (1940) therefore turned their attention to a derivative prepared in 1935, namely ' promin':—



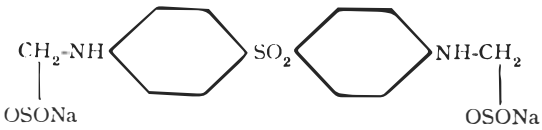
This is a N-N'-didextrose sulphonate of the parent substance with a molecular weight of 248 and a diaminodiphenylsulphone (DDS) content of 31.8 per cent. These workers reported that this substance had an inhibitory effect in experimental tuberculosis in guinea-pigs. This led to a further search for drugs in this group, not only for the treatment of tuberculosis, but also for leprosy—the other serious myco-bacterial infection which afflicts mankind. The following are the main derivatives of DDS which were prepared subsequent to the synthesis of 'promin' and have been advocated for the treatment of leprosy:—

(1) *Sulphetrone* (1936), a cinnamaldehyde bisulphite derivative of DDS:—



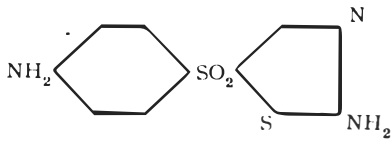
molecular weight 892.5, DDS content 27.8 percent.

(2) *Diasone.*—First prepared in 1938. This is a formaldehyde sulphoxulate derivative of DDS:—



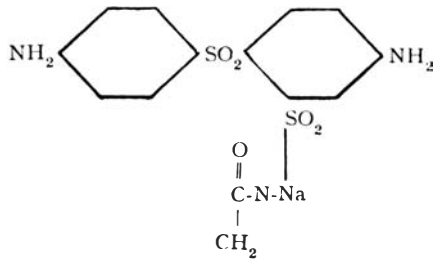
molecular weight 448, DDS content 55.4 per cent.

(3) *Promizole.*—This is a thiazole derivative of DDS in which, instead of a benzene ring, a thiazole group has been inserted:—



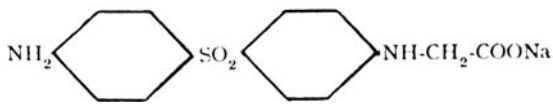
molecular weight 255, DDS content 97.5 per cent.

(4) *Promacetin.*—This is a sodium-4'-4'-diaminodiphenylsulphone-2-acetyl sulphonamide:—



molecular weight 390, DDS content 63.6 per cent.

(5) *Sulphone Cilag.*—This is a monoacetyl ester of DDS:—



molecular weight 328.8, DDS content 75.7 per cent.

As a result of work on the use of DDS in veterinary medicine (McEwen *et al.*, 1941) and the stimulus of contact with Francis, experiments were started in Madras in 1946, and subsequently in West Africa and Calcutta, to reinvestigate the possibility of giving DDS in preference to the more complex sulphones. The reasons for the continued advocacy of the complex sulphone derivatives will be explained when the individual drugs are discussed. It is sufficient to say that under certain conditions it has been shown by Lowe (1950) that the parent substance is possible of administration on a large scale, and therefore the original hope of the early workers that DDS would prove to be a powerful antibacterial drug has been largely fulfilled.

It was only natural that when the sulphones were found to be effective in leprosy, trials would be made of drugs which have been shown to have a chemotherapeutic effect in tuberculosis. Ryrie (1950) published a report on the treatment of leprosy by ' thiacetazone '. Behnisch *et al.* (1950) synthesized this drug, which has no relationship chemically to the sulphones or the sulphonamides. It is *para*-acetylamino-benzaldehyde thiosemicarbazone and has the following structural formula:—

SULPHONE THERAPY: DRUGS AND DOSAGE

Sulphetrone.—Both at the International Leprosy Congress at Havana and at the recent All-India Leprosy Congress, ' sulphetrone ' was recommended as the sulphone preparation which was likely to show the minimum toxic effects. Since the International Leprosy Congress, work has been continued in Madras and Calcutta on the parenteral administration of sulphetrone, and this has become the preparation of choice when parenteral, rather than oral, administration is advocated.

Dosage recommended: Whilst the All-India Leprosy Conference recommended a standard dosage of 4 g. per week, recent evidence in the Research Department of the Government Lady Willingdon Leprosy Sanatorium, Chingleput, indicates that a dosage of 3 g. per week is effective both clinically as well as bacteriologically. Sulphetrone is made up in a 50 per cent. solution in distilled water or freshly collected rain water, and can either be autoclaved or boiled. Carbolic acid, 0.5 per cent., or another antiseptic, is added if the solution is to be kept. If the worker has experience in the treatment of leprosy and can recognize the type of case which tends to react, then the following course of treatment is recommended:—

1 ml. of a 50 per cent solution of sulphetrone twice a week (1 g.)

increasing by 1 ml. per week until 3 ml. twice a week (3 g.) is reached.

If the practitioner has had little experience in the treatment of leprosy by the sulphone group of drugs, then the increase in dosage should be more gradual and should be given after one month's treatment on the lower dosage. Patients may complain

of pain on injection with a 50 per cent. solution of sulphetrone. If this is the case one or two expedients can be adopted: (1) reduce the percentage of the drug to 20 per cent. and give a greater quantity of the solution in order to administer the dose indicated above; (2) neutralize the solution, as the Calcutta workers (Dharmendra, 1950) have suggested, with sodium carbonate in the proportion of 1.4 g. of sodium carbonate to 1000 ml. of aqueous sulphetrone.

Oral administration of sulphetrone: Wharton (1947) first showed that sulphetrone given by the oral route was an effective drug in the treatment of lepromatous leprosy. Since then much work has been done and, generally speaking, the dosages now advocated are much lower than those formerly recommended. Nevertheless, now that greater experience has been gained with the parent substance, if oral therapy appears to be the best method of treatment DDS tablets should usually be given. Many, however, will still prefer to use sulphetrone, and therefore the following course is recommended:—

Two tablets (1 g.) per day for one week
Four tablets (2 g.) per day for one week
Six tablets (3 g.) daily

In areas where dietetic deficiencies are marked, it is well to increase the dose at a fortnightly, rather than weekly, interval.

Diasone.—The following is the recommended dosage of this drug:—

1 tablet (0.3 g.) once a day for 1 week
1 tablet (0.3 g.) twice a day for 1 week
1 tablet (0.3 g.) three times a day

Diaminodiphenylsulphone.—As a result of the work in Madras (Cochrane *et al.*, 1949) followed by that in Malaya (Molesworth *et al.*, 1949), it was shown that parenteral DDS was an effective form of treatment in leprosy. The original dosage used (2.5 g. per week) was found to be too high and, in addition, there was a general tendency to depot formation. Workers in Malaya, however, by administering a dosage of not greater than 1 g. per week, and using cocoanut oil as the suspending medium, have to a large extent overcome these two disadvantages of parenteral therapy. Since Lowe and Smith (1949) showed that DDS was almost completely absorbed when given by mouth, it is now generally recommended that DDS be given by this route rather than by injection. As will be mentioned, because of the great risk of toxicity in dosages higher than 600 mg. per week, oral DDS is not personally

recommended unless adequate supervision is possible and precautions taken to see that patients cannot take more than the prescribed dose. This means that unless the leprosy patients are in camps where a responsible individual can give personal supervision to the administration of daily oral treatment, this is not advocated, for it has been shown that bi-weekly medication may be as effective as daily dosage. The following is therefore the course of treatment recommended (a) for daily administration and (b) for bi-weekly administration:—

(a) Daily administration:—

½ tablet (50 mg.) per day for six days in the week (total weekly dose 300 mg.)
1 tablet (100 mg.) per day for six days in the week

It is inadvisable to increase the dose above 600 mg. per week. It is usually recommended to increase to the higher dose after fourteen days, but one month is a safer interval.

(b) Bi-weekly administration:—

1 tablet (100 mg.) twice a week for two weeks
2 tablets (200 mg.) twice a week for two weeks
3 tablets (300 mg.) twice a week

In certain areas, such as South India, where there is a great scarcity of food, it is wiser to increase the dosage each month rather than fortnightly.

Other derivatives.—It is impossible to discuss the dosages of all the derivatives of diaminodiphenylsulphone, and therefore those which are in more general use have been brought under review. It may be mentioned, however, that in the case of 'promin,' daily intravenous injections make it unsuitable for use. The expense of this, and of 'promacetin,' make these drugs impracticable for general administration. For general guidance it should be stated that the dosage of any given derivative of diaminodiphenylsulphone should be in proportion to its DDS content. Dosages in children should be proportionate—children of twelve years and under should receive half the adult dose, and those under seven one-quarter. Children, however, appear to tolerate sulphones extremely well.

CHOICE OF THERAPY IN RELATION TO TYPE OF CASE

Now that the cost of sulphone therapy has been reduced to a reasonably low figure, every active lepromatous case should receive this therapy. Lowe (1950) claims that all tuberculoid

cases (the leprides) should be given sulphone therapy. In all active tuberculoid cases it is advisable to begin with sulphone therapy, but the indolent, slowly progressive tuberculoid lesion will not respond as dramatically as the more active lesions. If marked improvement is not seen after eight months it is our practice to resort to intradermal injections of ethyl esters of hydnocarpus oil.

In the Indian with early hypopigmented macules of neural leprosy (maculo-anæsthetic lesions) there is little evidence that these drugs are efficacious. In neural leprosy with deformity or threatened deformity, sulphone therapy may be harmful in that the acute nerve pain which is sometimes seen may increase the nerve damage and therefore intensify the deformity. In these cases, orthopædic and physiotherapeutic measures will do more good than sulphone therapy. We believe that apart from the tuberculoid case, sulphone therapy should be used only in the bacteriologically positive case and that standard methods of hydnocarpus treatment should be employed in all other cases, with due attention to prevention and alleviation of deformity and trophic ulceration.

TOXIC REACTIONS TO SULPHONE THERAPY

All sulphones, be they ' promin,' ' diasone,' ' sulphetrone ' or the parent substance DDS, are liable to set up a condition which has been described by Wolcott (1947) as *erythema nodosum leprosum*. This syndrome was known previous to sulphone therapy, but since its introduction it has become much more common. It is probably related to the Herxheimer reaction and represents an acute response to the rapid multiplication and breaking down of *M. lepræ*, giving rise to high fever, erythematous (rose spot) nodules, and erythema-nodosum-like lesions. The condition is on the whole favourable, and only calls for the stoppage of the drugs if the reaction is severe. If sulphones are stopped, then half the dose which precipitated this condition should be given after the temperature has returned to normal and all signs have subsided. This condition must not be confused with an extension of activity of the disease which shows itself in fresh lesions, sometimes vesicles which show pus, or breaking-down nodules. Unlike the erythema nodosum phenomenon, in which few or no bacilli are found, bacilli are seen in enormous numbers and often in ' globus ' formation. Such a condition demands the immediate stoppage of the drug and very gradual increase on resumption of treatment.

The parent sulphone has the greatest tendency to precipitate these conditions, and parenteral ' sulphetrone ' the least.

Blood changes.—The most common toxic sign is a decrease in the red cell count and a parallel decrease in the hæmoglobin value. With the parent substance—orally or parenterally—and with promin *intravenously*, diasone and sulphetrone given orally, this tendency to anæmia may be serious and a considerable fall in both the red cell count and hæmoglobin value may be seen. A serious fall in these figures has not been noted when sulphetrone is given parenterally. A general rule is that (except in the case of sulphetrone given parenterally) if the hæmoglobin is below 12 g., then hæmatinics should be administered, and if below 10 g., then yeast should be given in addition and the drug stopped. In this case sulphone therapy should be resumed when the hæmoglobin reaches 13 to 14 g. Slight depression in the hæmoglobin value in the tropics is not an indication to withhold therapy, and it must be remembered that, when large numbers are treated, the necessity for giving additional iron therapy increases both the complexity of administration and the cost of treatment.

If the dosages advocated are strictly adhered to, the more serious toxic signs such as *nausea, vomiting, jaundice,* and *confusional mental states,* are unlikely to occur. Nevertheless, with DDS therapy the urine should be tested periodically for urobilin.

With oral remedies, such as 'diasone' and 'sulphetrone', *gastric disturbances* may be seen. These are seldom troublesome on the smaller dose which is herein advocated. Generally speaking, when the initial dose is small and the increase in dosage gradual, little difficulty is experienced in respect to toxic signs, but again DDS is most liable to cause toxic manifestations. The only toxic manifestation of any moment with aqueous sulphetrone is a *drug dermatitis,* which usually responds to antihistaminics.

METHOD OF ACTION OF THE SULPHONE DRUGS

It has been surmised that the action of the chemotherapeutic agencies is probably due to interference with the utilization of an essential metabolite, and thus the multiplication of the organism in the tissues is inhibited. It is well known that all sulphones have the property of causing the *M. lepræ* to break up into granules, and it is suggested that these are seen when the environment is unfavourable to the growth of the organism. Granular forms, however, are not only seen in sulphone therapy, for there is evidence that this also occurs under hydnocarpus therapy, as well as during the ordinary evolution of the disease. In this connexion it should be mentioned that Khanolkar (1951) has demonstrated that positive contacts of open cases not only occasionally show a few

bacilli in sections of the skin, but these bacilli tend to break up into granules and are finally reduced to acid-fast dust ('fuchsinophil material'). Another phenomenon which is noted is that when the bacilli are markedly reduced to the granular form the clinical signs subside, sometimes most dramatically. Under these conditions the granuloma gradually begins to clear from the dermis. In an advanced lepromatous case, enormous numbers of bacilli can be demonstrated in skin sections, and to see after eighteen months to two years the almost complete disappearance of the granulomatous tissue is most striking. De Souza Lima's (1948) observation has been confirmed independently in material taken from cases in Madras (Cochrane, 1951) that when the bacilli disappear from the skin, granular forms are often seen in the small subcutaneous nerves and in the muscles (? nerve endings), and the histology returns to that of the uncharacteristic (pre-leproma) appearance of the very early lesion. This observation—that the bacilli in many cases persist in the nerves and muscles after they have disappeared from the dermis—suggests that these organs may act as reservoirs of infection from which a recrudescence of the disease is always possible.

It is therefore believed that there is sufficient evidence to conclude that these granular forms of *M. Lepræ* are viable. It is probable that they are inactive, and the patient may be non-infective when only a few granules are left. It is known, however, that lepra reactions can occur even after the bacilli have almost completely disappeared, using standard methods of examination.

I have seen severe lepra reactions in a patient who previously showed an occasional negative smear, and then a few smears revealing a few acid-fast granules, suddenly pass into a state of severe reaction, and after this had subsided the smear results deteriorated; nevertheless, all bacilli were still granular. In one case, which showed only acid-fast granules when treatment was discontinued, acid-fast rods began to appear in the smears eighteen months after the cessation of treatment.

From these observations it seems that the acid-fast granules are still viable forms of the bacillus, even though they may ultimately be destroyed by macrophages. The following tentative conclusions therefore suggest themselves:—

(1) Although there is at present no definite evidence that the granular forms of bacilli are dead, in all probability they represent a stage of relative inactivity and are therefore much less capable of transmitting the infection.

(2) The sulphones prepare the tissues of the body for the alteration of the bacilli to granular forms and thus enable the

macrophages to deal with them more easily. Whether or not a given individual will lose all signs of bacilli may depend upon the inherent capability of the body to dispose of these granules. The number of cases which became histologically negative, that is, those in which the granular forms cannot be found even in small subcutaneous nerves, is not yet known.

(3) In view of these findings it might be well to continue maintenance doses of sulphones for a considerable time after 'clinical cure', and possibly throughout the life of the patient.

There are a number of anomalies in sulphone therapy which still need elucidation. For instance, it may not be correct to state that because a lepromatous case is given sulphone therapy early that it will become negative more quickly than one which is more advanced. I have seen marked clinical and bacteriological improvement in moderately advanced and advanced lepromatous cases, whereas in the earlier cases the progress has been much slower. In several cases, although only a few smears were slightly positive, these have remained in this state for over two years, during which period more advanced cases have become negative. The explanation for this may be, as pointed out, due to the variableness in the individual to dispose of the granular forms of the bacilli.

OTHER CHEMOTHERAPEUTIC AGENTS

This account of the chemotherapy of leprosy would not be complete without some reference to other chemotherapeutic agents and antibiotics—namely, thiacetazone, *para*-aminosalicylic acid, and streptomycin.

(1) *Thiacetazone.*—Whilst it has not been possible to confirm Ryrie's (1950) observations that thiacetazone has a quicker action on the *M. lepræ* than the sulphones, yet the action of these drugs is similar, and there is evidence that it is an effective agent in the treatment of leprosy, and is worth a trial in those cases which show intolerance to sulphones, especially those which exhibit a drug dermatitis. The dosage which has been used is 25 mg. daily, increasing each week by 25 mg. until 150 mg. per day is reached. Children of twelve years and under receive half this dose. Under this regimen moderately satisfactory progress has been seen in the majority of cases treated over a period of nine months.

(2) *Para-aminosalicylic acid and streptomycin.*—Although there is evidence that PAS and streptomycin have a similar action to the sulphones, this is so slow that the expense of the drug and the

necessity for frequent administration preclude their being used in leprosy. There is no evidence that these drugs can control lepra reaction; both drugs—PAS to a greater extent than streptomycin—may precipitate an acute exacerbation of the disease as well as the phenomenon known as erythema nodosum leprosum.

CONCLUSION

In closing, readers are reminded of the danger of assuming that the leprosy problem is now solved because of the development of a highly successful therapy. It would be a retrograde step if old slogans of twenty-five or more years ago were revived. Caution should still be the watchword in relation to statements concerning the absolute success of modern therapy in leprosy.

The new and welcome advances in treatment have served to focus attention to a greater extent on the need for the study of physiotherapy and orthopædic measures (including surgery) in leprosy, so that deformity—threatened or actual—may be relieved and the leprosy patient, if 'cured' by sulphone, or other therapy, can resume his normal activities without disabling deformity.

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