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## THE SULPHONE TREATMENT OF LEPROSY*

by

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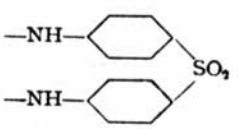
The drugs commonly known as sulphones are derivatives of diaminodiphenyl sulphone.




It was their antibiotic effect in controlling the growth of *M. tuberculosis* in experimental animals and *in vitro* (Feldman *et al.*, 1942; Petter and Prenzlau, 1944) that first suggested trial in leprosy. Strangely, they have so far shown much more evidence of usefulness in leprosy than in tuberculosis.

The sulphone derivatives which have so far been tried in leprosy are "promin" (U.S.A., "promin"; in England, "promanide") (diaminodiphenyl sulphone-*nn*-didextrose sulphonate), "diasone" (disodiumformaldehyde sulphoxylate of diaminodiphenyl sulphone), "promizol" (2,4'-diamino-5-thiasolylphenyl sulphone), and "sulphetrone" (tetrasodium phenylpropylamino-diphenyl-sulphone tetrasulphonate). Promin was first used in the National Leprosarium, Carville, U.S.A. (Faget *et al.*, 1943). It was found to be excessively toxic by oral administration but to be tolerated intravenously in daily doses up to 5 g. Following on the first published results on promin, Muir (1944) began a trial of diasone in Trinidad. Fearing that diasone might be toxic by mouth like promin, he first gave it intravenously, but later found that it was well tolerated orally in daily doses up to 2 g. A more recent sulphone derivative, promizole, is considered by the Carville workers (Faget, Pogge and Johansen, 1946) to give possibly even better results than the first

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two preparations, though it has not yet been tried out sufficiently. This can be given orally in daily doses up to 6 g. Lastly, sulphetrone (B.W. & Co.) is under trial, and the first reports indicate promising results.

The results obtained with these sulphones appear to be similar, though they may vary in the degree of toxicity, the amount of the effective dose, and the speed of results.

### MODE OF ADMINISTRATION

*Suitable Type of Case.*—It is the lepromatous or severe type of leprosy to which sulphone treatment has been applied — that is to say, the type which so far has been least amenable to treatment by chaulmoogra and other drugs. I have had no experience with sulphones in tuberculoid and uncharacteristic cases, nor have I seen any published results in these types.

*Toxic Effects.*—Faget *et al.* (1943) mention the following toxic signs as occurring: decrease in blood cells, leucopenia, allergic dermatitis, allergic rhinitis, mild and ephemeral headaches and nausea, and lepra reaction including iridocyclitis. Further observation has, however, shown that with suitable dosage most of these can be avoided. In my experience anaemia (chiefly due to destruction of red cells) and increased reactionary exacerbations are the two toxic indications to be guarded against, and these are apt to occur principally in patients in poor general health and/or in an advanced stage of the lepromatous type, and in the initial stages of treatment. Before beginning treatment the patient should be examined for anaemia, and when this is present, as it often is in severe lepromatous cases, a preliminary course of full doses of ferrous sulphate or carbonate should be given.

*Dosage.*—My own experience has been chiefly with diasone (Muir, 1944, 1946), and the dosage here described is what is recommended in the use of this drug. Considerably higher doses have been used with promin and promizole (Faget *et al.*, 1943, 1946). It is advisable to begin with small doses in all cases, and gradually raise the amount according to the tolerance of the patient. In doing this the important indications are: the stage of the disease; the general condition of the patient, especially as regards febrile and focal reactionary signs; the condition of the blood; and the presence of anaemia. If the haemoglobin percentage is below 70 a preliminary course of iron should be given, and if this is not effective injections of liver extract should be added.

Diasone is generally made up in 5-gr. (0.32 g.) capsules or tab-

lets. When the haemoglobin is at or over 70%, begin with 1, 2, or 3 tablets according to the general condition of the patient. This should be taken in one undivided dose, preferably an hour after food, so as to promote quick absorption and the highest blood concentration. Reactionary signs are not a contraindication to beginning the treatment, but are a warning not to raise the dose too rapidly. Whatever the initial dose, repeat it every second day for the first week unless there are signs of exacerbation. In strong early cases without septic or other complications one tablet may be added after the first week on the intermediate days and increased gradually till, after three or four weeks, the patient is taking 3 tablets daily for six days a week. It may, however, be a considerable time before a weaker or more advanced case reaches this dosage. The haemoglobin should be tested every week to begin with and iron (and if necessary liver extract) continued in all cases with a percentage below 80 or 90. A fall below 70% or the intercurrence of increased reaction calls for temporary suspension of diasone or diminution of the dose. When a dose of 3 tablets a day for six days a week has been reached it is well to suspend treatment for one week every month. Apparently when full dosage is suddenly resumed after this temporary stoppage the blood concentration rises to a higher level for a time. In patients who have improved and are free from signs of anaemia and reaction the dose may be gradually raised to 6 tablets daily six days a week for three weeks a month—this being regarded as the maximum average dose, though it may be increased or diminished according to the body weight of the patient.

### EFFECTS OF TREATMENT

These vary according to the stage of the disease. In a severe advanced lepromatous case with ulcerating leproma of the limbs, ulceration of the nasal and other mucous membranes with obstruction of breathing, and with severely affected eyes going on to blindness, the first effects, which often take place within a few weeks, are the healing of ulcers, clearing of the nose, and arrest of the eye condition with improved vision.

The next effect is seen in patients with chronic or subacute allergic reactions indicated by slight rise of temperature and/or the frequent appearance and subsidence of nodules and other inflammatory skin lesions; these symptoms gradually subside. At the same time permanent nodules and other raised skin elevations become slowly absorbed and flattened out, leaving marked wrinkling

of the integument. This improvement generally requires a few months.

The third stage in recovery, and the only one in early or less advanced cases, is the gradual lessening of the number of bacilli found in sections and smears from the skin and in smears from the nose. Thus three-plus cases become two-plus and then one-plus, and one-plus cases become negative. The time required for this appears to vary with the advancement of the disease: some early cases have become negative in four or six months, but more advanced cases may require four, five, or even more years. One of the most striking signs of improvement is that seen in the affected eye and especially in the cornea, where, because of its transparency, the arrest and a certain amount of recession of the lepromatous infiltration can be observed with a lens or corneal microscope.

There is one important point on which evidence is not yet available — that is, whether or not a point is reached at which the type changes, the lepromatous case being transformed into a tuberculoid one with a negative "lepromin" test becoming positive. Theoretically the lepromin test is negative in the lepromatous case because the antigen (i.e., lepra bacilli) is in such great excess of antibodies formed that an effective allergic reaction, which would destroy the bacilli, cannot take place. As the bacillary antigen becomes less and less, is a point reached at which an effective reaction can take place? If so, it would be indicated by a positive lepromin reaction, and we should have an additional factor helping to clear up the residual bacilli. I have found indications in one or two cases that this may occur to some extent, but further evidence is needed.

### LENGTH OF TREATMENT

In any case, treatment should be continued at least until repeated bacterioscopic examinations have given negative results over a period of six months to two years, varying directly with the advance of the disease at the beginning of treatment, and with the length of treatment required to produce the first negative bacterioscopic results. Faget (1947) reports that "19 promin-treated patients have been discharged as disease-arrested following twelve consecutive months of negative bacterioscopy. Of this number three were under treatment for 1½ to 2 years, three from 2 to 3 years, six from 3 to 4 years, and seven from 4 to 5 years. There have been no relapses. . . . The period of observation following arrest of the disease has varied from a few months to 2½ years."

Iodides have a specific effect in showing up concealed lepromatous foci. It is possible that their careful administration in cases

that have become bacterioscopically negative may be of use in determining the length of further treatment required, and perhaps in speeding up the elimination of residual foci; but this matter still calls for very careful investigation.

*Regulation of Established Treatment.*—Particulars have been given of the dangers attending the initial treatment with diasone. But once the patient has taken his maximum dose for a few months without diminution of haemoglobin content or reactionary symptoms, and has made definite improvement as regards both leprosy and in his general health, the same precautionary methods cease to be necessary and treatment may be continued by an intelligent and reliable patient with a minimum of supervision. A visit by the doctor once a month is often all that is needed. This fact is particularly helpful to patients under domiciliary treatment.

## MODE OF ACTION

It is still uncertain how the sulphones act. Fite and Gemar (1946), after examination of biopsy sections from 32 patients under promin, concluded that tissue changes are "atrophic in character with extremely slow and gradual lessening of numbers of organisms in the lesions to the point of final disappearance in 10 of 32 cases examined. . . . The important finding is that promin appears to eliminate bacillary infection of the blood vessels and blood stream, thereby preventing the formation of new lesions. The atrophy of focal lesions is also more apparent in areas with a more generous blood supply. The results indicate strongly that the best results may be expected in those cases in which treatment is begun in a comparatively early stage of the disease."

A satisfactory hypothesis is as follows. Ordinarily in lepromatous cases the cellular ingestion of bacilli and their multiplication in the cytoplasm result in the formation of "globi," the rounded masses of bacilli found in any typical lepromatous cases. The global bacilli gradually die and are transformed into a non-acid-fast lipoid matrix which imbeds the still acid-fast bacilli. Thus in untreated cases the living bacillary element in a globus gradually becomes extinct, and its place is normally taken by fresh globi. It may be supposed that the sulphones act not by destroying bacilli but by preventing the multiplication of bacilli and the formation of fresh globi.

If this hypothesis is correct it would account for: (*a*) The finding of globi in smears from the nose and skin of treated patients, in which there are no acid-fast bacilli or in which the bacilli are thin and ghost-like. (*b*) The long time required in the clearing up of bacilli in fairly advanced cases. This will be made clear when it is

mentioned that human leprosy bacilli, killed by boiling and injected into rats, can still be found retaining their acid-fastness after 18 months.

### THE FUTURE OF SULPHONE TREATMENT

The history of leprosy in the last 30 or 40 years is strewn with the wrecks of so-called "cures." Knowing this, one is hesitant to put forward claims for the sulphones which might fail to be confirmed. It will take years before we can say with any confidence what the final results are, whether a complete and lasting cure is possible, what is the relapse rate, and whether relapsed cases will yield to further courses of treatment.

Confidence is given, however, by the fact that experienced workers all over the world who have carried out the initial trials have without exception obtained favourable results such as they had never found with other remedies. Many have reported definite improvement in practically all cases that have been under treatment for at least six months.

The history of a rising scale of effectiveness in other drugs, such as the sulphonamides, gives reason for hope that sulphone derivatives may be produced which will give even more rapid and effective results.

### SULPHONES AND THE ANTI-LEPROSY CAMPAIGN

*The Supply of the Drugs.*—Few of the countries where leprosy is rife are wealthy, and the patients who require treatment most are as a rule the poorest of the poor. In a campaign against leprosy there is, therefore, need for a drug which is not only effective but which can be made available to the poorest patient in countries like Africa, India, and China.

Fortunately the raw material of the sulphones is not expensive, and although the outlay on manufacture must at first be considerable the cost should rapidly diminish with mass production. It is calculated that 1,000 5-gr. (0.32-g.) tablets of diasone should, on an average, suffice for one patient for one year, and the present cost of this is in the region of £6. If treatment is to be extended to a gradually increasing proportion of the one or two million lepromatous cases calculated to exist in the world, there will be a considerable call on the budgets of governments, and on the generosity of philanthropic bodies.

*Effect on Control.*—The two chief difficulties in the control of leprosy have been: (*a*) open infectious cases, through ignorance, fear, and shame, or want of opportunity, are not isolated until they

have had a chance, often lasting several years, of spreading the disease to their relations and other contacts; (*b*) that the treatment available has been painful and hard to persist with over a long period and, even when persisted with, has in the majority of lepromatous cases been unable to arrest the disease.

It may be expected that once the effects of sulphones become widely known they will attract early cases which would otherwise have concealed the disease as long as possible. Thus to a gradually increasing extent the danger of infection should be cut off at its source.

*Need of Personnel.*—One of the chief difficulties in anti-leprosy work has always been the lack of doctors. In the medical profession there has been a prejudice against leprosy, either on account of fear or because it was considered that so little could be done for it. In Brazil the Government offers an extra allowance beyond the ordinary service rates. But the best work has always been done by those who have felt they have a vocation, and many such doctors and other workers, once they have overcome the prejudices which surround the subject of leprosy, have become enthralled by the interest of the work. Now that there is a clearer prospect of effective treatment and control, it is to be hoped that more doctors with a pioneering and venturesome (not to say philanthropic) spirit will offer to do this work.

SUMMARY

The sulphones have been found of definite benefit in the severe or lepromatous type of leprosy, clearing of complications, causing a slow but steady diminution of the bacilli, and in some cases bringing about arrest of the disease.

The method of administration of diasone, its possible mode of action, and length of treatment are given in detail.

The effects of sulphone treatment on the campaign against leprosy, the supply of sulphones, and the need of suitable personnel are discussed.

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