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LEPROSY REVIEW.

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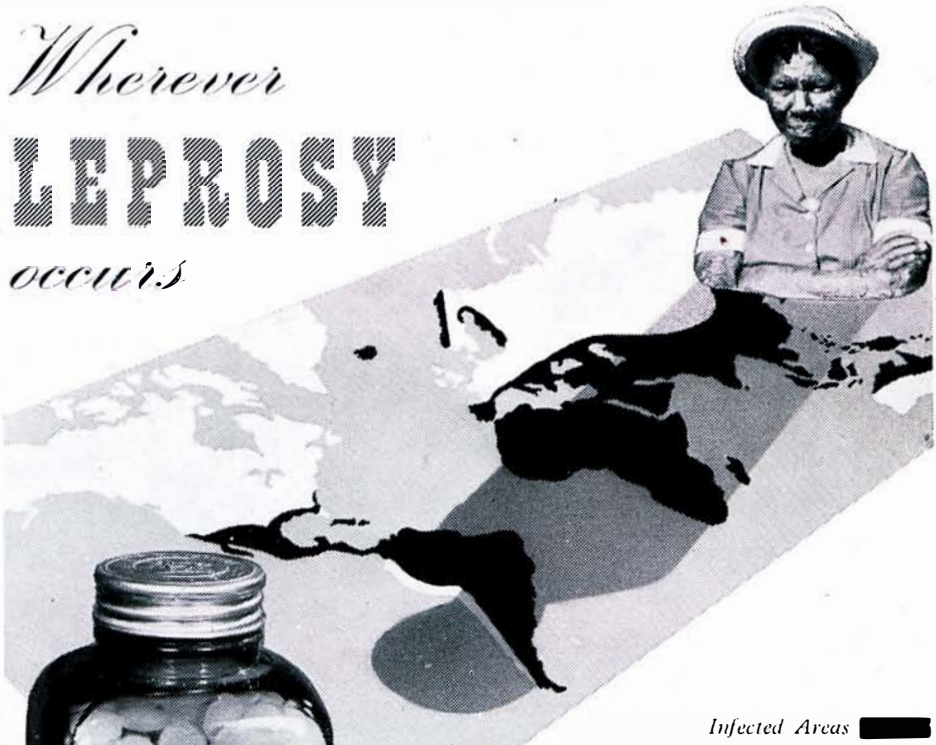
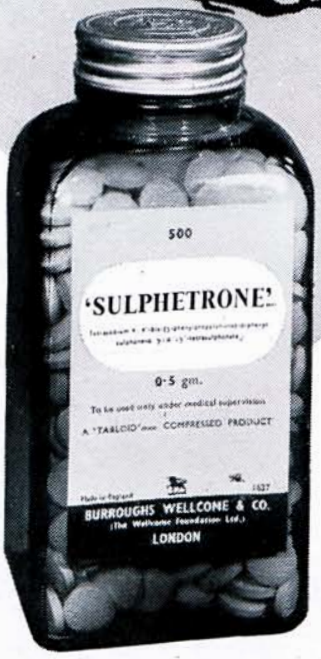
Wherever

LEPROSY

occurs





Throughout the world, leprologists are turning to 'Sulphetrone' as the most efficient known remedy for the treatment of leprosy. Reports stress that it produces clinical and bacteriological improvements with comparative absence of toxic effects. Its principal indication is lepromatous leprosy, but it may be used in any form of the disease. Ample supplies are available.

'SULPHETRONE'

BRAND

Tetrasodium 4 : 4'-bis-(γ-phenylpropylamino)-diphenylsulphone-α : γ : α' : γ'-tetrasulphonate

BURROUGHS WELLCOME & CO. *(The Wellcome Foundation Ltd.)* **LONDON**

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EDITORIAL

THE SULPHONES AT THE CROSS ROADS.

It is now accepted that the sulphone group of drugs constitute the therapy of choice in lepromatous leprosy. Besides this there is growing evidence that these drugs are of definite value in the treatment of the early indeterminate active macule, and in active tuberculoid leprosy. That is, we may assume tentatively that all forms of active leprosy are beneficially influenced by the sulphone drugs. It remains to be seen what influence this may have on our concept of the action of the sulphones.

Two claims are now being made which are of cardinal importance in leprosy therapy. One is that diaminodiphenylsulphone—the original basis on which the proprietary sulphones are built—can produce results on a dosage of half a gramme a week. The other is that the proprietary sulphones, promin, diasone, sulphetrone, etc., are broken up in the tissues with the release of the basic diaminodiphenylsulphone.

These two claims require the most careful consideration, and call for the most intense research. It would be difficult to overestimate their importance. If half a gramme a week of diaminodiphenylsulphone—a non-proprietary and relatively inexpensive compound—can produce therapeutic results comparable with much higher doses of the proprietary drugs, then a notable advance would seem to have been made. The claims made with regard to the retention of diaminodiphenylsulphone in the tissues are at present conflicting. Rapid elimination of the drug will presumably mean failure to exert its specific action. On the other hand, retention of diaminodiphenylsulphone in the tissues, even in relatively small quantities, means an outbreak of toxic symptoms. The long term action of small but cumulative doses of the drug has still to be ascertained. Diaminodiphenylsulphone is the cheapest of all the sulphones; it is also by far the most toxic.

The other claim is that the proprietary sulphones, by any method of administration, act by the release of basic diaminodiphenylsulphone. Is this true? If so, have the various modifications of the original drug no special benefit apart from acting as diluents, or possibly detoxicants, of the effective basic substance? The future of leprosy therapy and, to some extent, of leprosy control, depends on the answer to these questions.

It is evident that the blood or tissue concentration of sulphone is no certain indication of its therapeutic efficiency. Some cases improve with amazing rapidity; others take years. The biochemical answers are not necessarily the therapeutic answers. The time is indeed ripe for a qualified scientific study of the sulphone drugs.

TREATMENT WITH DIASONE — TWELVE MONTHS' EXPERIENCE WITH 22 PATIENTS— AN INTERIM REPORT

A. B. MACDONALD.

The following is an account of the treatment with diasone of 22 patients for twelve months beginning September, 1947.

The cases chosen were all lepromatous, and among the worst on the roll. Preference was given to those who were longest in the colony, a number of them being with us 15 to 20 years. These had been receiving " standard " treatment all the time, and had long been considered incurable. A well-known leprologist who visited us, and saw them, questioned if we could make anything of such patients. However, perhaps for sentimental reasons, these " old friends " got the first chance, and on the whole it has been justified. It is obvious of course that more spectacular results would have been obtained had the trial been made with early lepromatous cases. But again we find that early lepromatous cases do respond frequently to treatment with hydnocarpus oil and become negative. It was therefore desired to test the claim that diasone was effective in old-standing cases where hydnocarpus oil had definitely failed.

Each patient was given one tablet (0.3 grm) every second day, and then one every day, gradually increasing to four tablets daily seven days a week as a maximum where there was general improvement, no diminution in the percentage of haemoglobin, and no appearance of fresh nodules. If so, administration was stopped for two weeks, and then begun again. All have had Gr. 30 Ferri et Amm. Cit. b.i.d. from the commencement of treatment.

One man developed a severe conjunctivitis of the left eye, several had an outbreak of new nodules, which except in one case all subsided within two weeks.

In four patients the haemoglobin percentage diminished, and has not risen to date in spite of getting iron and liver therapy.

Small injections of hydnocarpus oil continued more or less for their psychological effect. As years of injections had little effect before, it follows that any improvement now could be credited to diasone.

RESULTS OF 22 CASES—ACTIVE AND ADVANCED.

Markedly improved	6
Moderately improved	6
Slightly improved	9
Slightly worse	1
	22

In general, with one exception, there was noticeable improvement, in six cases this being marked. The patients themselves were very pleased indeed; indeed they were pathetically hopeful, although it is surprising if many of them had not abandoned hope for some years. In almost every case the ulcers cleared up, the general health improved, the nodules flattened and decreased in size, while the macules faded. Those with nodular eyes were too far gone to show any striking improvement, but the laryngeal trouble which two of them had cleared up and the voice returned. Bacteriologically the skin in two patients became negative, the nose in one. In some the numbers of bacilli became less, while in others there was degeneration, and they seemed less "acid-fast." On the whole the results were encouraging, and certainly there *were* results, where before with hydnocarpus oil there were little or none. I have every hope that the improvement shown will continue with further administration of the drug.

The details are appended:—

CASE 1: REG. NO. 1120: MODERATELY ADVANCED, ACTIVE.

Sept. 1947: Entered Colony 1930, Male, aged 32. Was home for five years without permission. Generally diffused type with small nodules throughout skin. Has bright erythematous papules or macules occasionally which are sometimes positive on laboratory examination. These come and go after weeks, Skin became negative in 1944 and has remained so since apart from three temporary outbreaks. Has been a resistant case otherwise.

Laboratory report: SKIN 0/40, NOSE 40/1, S.R. 21, Hb. 60%.

Sept. 1948: General health has improved. Skin still shows some depigmentation, faint but active, the nodules have flattened and there has been no appearance recently of any erythematous papules. He is strong and well.

Laboratory report: SKIN 0/50, NOSE 0/50, S.R. 38, Hb. 90%—moderately improved.

CASE 2: REG. NO. 846: ADVANCED ACTIVE.

Sept. 1947: Entered colony 1932. Male, aged 14. Looked a reasonably promising case on arrival but during the last ten years has gone down hill very considerably. Face and ears very nodular. Skin covered with diffuse depigmentation throughout, main en griffe both hands. Legs show gross trophic changes with many small coalescing erythematous patches. Has ulcers on legs and sole of left foot, apparently a hopeless incurable case.

Laboratory report: SKIN M/1, NOSE M/1, S.R.42, Hb. 50%.

Sept. 1948: Ulcers have all healed up. Nodules have partly subsided but face is last to change and looks still active and erythematous. Raised thickenings on legs have gone down. Erythema elsewhere than on face has faded.

Laboratory report: SKIN M/1, NOSE 40/1, S.R.57, Hb. 55% —slight improvement.

CASE 3: REG. NO. 961: ADVANCED ACTIVE.

Sept. 1947: Admitted to colony 1928. Male, aged 25. Was away for one year. Has gradually deteriorated. Complete depigmentation of skin seems to have taken place. Has always been bacteriologically positive. Ears nodular and there are a few nodules scattered on trunk. He has always been reasonably strong and able to work.

Laboratory report: SKIN M/1, NOSE M/1, S.R. 39, Hb. 65%.

Sept. 1948: Improved. Feels better. Had new lepromatous spreading macules on face and trunk which lasted for four weeks and then subsided. During this period treatment was suspended. Other nodules have all gone down. The skin generally is less active. He has more sensation in his legs.

Laboratory report: SKIN 10/1, NOSE 60/1, S.R. 20, Hb. 98% —moderately improved.

CASE 4: REG. NO. 4462: MODERATELY ADVANCED—ACTIVE.

Sept. 1947: Admitted 1940. Male, aged 12. Has shown improvement since admission but still positive skin and nose. Has

still nodules on ears, flattened nodules on face and some on legs, with general erythema of skin. Looks still an active case.

Laboratory report: SKIN 30/1, NOSE M/1, S.R. 30, Hb. 60%.

Sept. 1948: All nodules have subsided, the erythema has faded, the ears are almost normal. He is strong and well.

Laboratory report: SKIN 0/50, NOSE 30/1, S.R. 46, Hb. 80% —markedly improved.

CASE 5: REG. NO. 73: ADVANCED ACTIVE.

Sept. 1947: Admitted 1927, Male, aged 20. This is the oldest case in the colony, being here 20 years with some intervals at home. Now is very advanced, nodules all over face, coalescing nodules on limbs, legs show gross trophic changes with breaking down of skin and shallow ulceration. The skin is permanently depigmented. The left eye is nodular, and the sight in this eye is lost. The larynx is affected and he has aphonia. In spite of all this he usually is able to carry on his trade as a carpenter.

Laboratory report: SKIN M/1, NOSE M/1, SR. 53, Hb. 60%.

Sept. 1948: Has shown improvement, the nodules have subsided considerably and the ulcers all healed up. The skin is not nearly so erythematous as it was. The left eye remains unchanged.

Laboratory report: SKIN M/1, NOSE M/1, S.R. 28, Hb. 75% —moderately improved.

CASE 6: REG. NO. 828: ACTIVE ADVANCED.

Sept. 1947: Admitted 1931 as boy of 14 years. Had diffuse depigmentation affecting entire skin. Ears nodular, and there are large nodules on legs and arms. Skin shows gross trophic changes in legs, with diffuse thickenings and skin breaking in parts forming ulcers. The left eye is blind with nodulation and keratitis. He suffers from aphonia. Is anaemic—R.B.C. 2,750,000. W.B.C. 8,200.

Laboratory report: SKIN M/1, NOSE M/1, SR. 42, Hb. 50%.

Sept. 1948: The nodules have somewhat subsided, the ulcers have healed, his voice has returned, the general health has improved, the left eye is unchanged.

Laboratory report: SKIN M/1, NOSE M/1, S.R. 70, Hb. 50% —slightly improved.

R.B.C. 2,790,000, W.B.C. 10,200.

CASE 7: REG. NO. 1371: ACTIVE ADVANCED.

Sept. 1947: Admitted 1931, Male. Was home for five years. Gross depigmentation throughout with slight nodulation of ears. Had removal of metatarsal bone following ulceration. Still has ulcer on heel and one on great toe.

Laboratory report: SKIN 60/1, NOSE 10/1, SR. 85, Hb. 85%.

Sept. 1948: Skin has improved. Nodules on ears are reduced in size. Had ulcer below great toe and heel. Part of calcaneous bone removed. Was in hospital for some weeks during which treatment was stopped Has had on two occasions conjunctivitis. Ulcer is now healing up. He feels better and certainly looks it. The skin is now negative but still erythematous.

Laboratory report: SKIN 0/50, NOSE M/1, S.R. 20, Hb. 95% —slightly improved.

CASE 8: REG. NO. 2519: ACTIVE ADVANCED.

Sept. 1947: Admitted 1933, aged 35. Was home 3 years. Has got gradually worse and suffers from anaemia. Skin shows general diffuse depigmentation. Abdomen is covered with very large thick coalescing nodules. There are also nodules on face, ears, back and legs. Feet show some ulceration,

Laboratory report: SKIN M/1, NOSE M/1, SR. 55, Hb. 45%. R.B.C. 3,240,000, W.B.C. 5,600.

Sept. 1948: Anaemia has become worse—now 30%. He reached three tablets of Diasone but this had to be reduced to one daily. The nodules on abdomen are going down, the depigmentation of skin is less. The ulcers on feet have healed.

Laboratory report: SKIN M/1, NOSE M/1, SR. 39, Hb. 30% —slightly improved.
R.B.C. 1,690,000, W.B.C. 9,200.

CASE 9: REG. NO. 3347: ACTIVE ADVANCED.

Sept. 1947: Admitted 1937, Male, aged 45. Complete depigmentation of skin, with nodules on ears and scattered throughout body. Very active. Has had numerous leprotic reactions and looks an incurable case. Had an ulcer below left great toe.

Laboratory report: SKIN 80/1, NOSE M/1, SR. 25, Hb. 60%.

Sept. 1948: He feels better and more active, the nodules have diminished in size, the ulcer has healed. Has suffered from conjunctivitis of left eye. Looks still an active lepromatous case.

Laboratory report: SKIN M/1, NOSE M/1, SR. 35, Hb. 70% —slightly improved.

CASE 10: REG. NO. 3487: ACTIVE ADVANCED.

Sept. 1947: Admitted 1937, Male, aged 13. Skin depigmented throughout with gross trophic changes in legs with ulceration, has flattened nodules on face and on arms and legs. There are various patches of depigmentation throughout skin. He is a debilitated subject, and anaemic.

Laboratoryr eport: SKIN M/1, NOSE M/1, SR. 65, Hb. 55%. R.B.C. 2,850,000, W.B.C. 5,800.

Sept. 1948: Some improvement has taken place, the nodules on the face have subsided to some extent. The nodules on the legs seem to be stationary, and he complains of neuritis of his legs. The ulceration on legs has finished.

Laboratory report: SKIN M/1, NOSE M/1, SR. 62, Hb. 58% —slightly improved.
R.B.C. 2,910,000, W.B.C. 9,400.

CASE 11: REG. NO. 1960: ACTIVE ADVANCED.

Sept. 1947: Admitted 1932, male, aged 25. Has steadily deteriorated. There are nodules and gross depigmentation throughout body. The distal phalanges of all fingers have ulcerated off. He has had several operations for the extirpation of meta-tarsals. He is always developing a new ulcer. Apparently an incurable case, and is incapable of work—R.B.C. 3,680,000.

Laboratory report: SKIN M/1, NOSE M/1, SR. 40, Hb. 55%.

Sept. 1948: There has been some improvement, and he is now able to walk about and do some light work, the nodules have become reduced in size and the skin looks less active. On the hands the ulcers have healed up, and the feet are improving. The anaemia is less.

Laboratory report: SKIN M/1, NOSE M/1, SR. 22, Hb. 65% slightly improved.

CASE 12: REG. NO. 1150: ACTIVE ADVANCED.

Sept. 1947: Admitted 1929 as small boy, entire skin had changed following depigmentation. Was discharged 1938 but re-admitted 1942 with active nodular leprosy — very disappointing case. There are nodules on face and scattered throughout body, and gross trophic changes in legs with widespread thickenings. He suffers from anaemia—R.B.C. 2,870,000, W.B.C. 4,760.

Laboratory report: SKIN M/1, NOSE M/1, SR. , Hb. 55%.

Sept. 1948: More nodules appeared on arms but subcutaneous and of temporary duration. Those on the surface of the skin have subsided. He feels better he says, but is still an active lepromatous case. Has been getting latterly two tablets per day.

Laboratory report: SKIN M/1, NOSE 60/1, Hb. 52%—slightly improved.
R.B.C. 3,170,000, W.B.C. 12,800.

CASE 13: REG. NO. 860: ACTIVE ADVANCE.

Sept. 1947: Admitted as small boy in 1932. Generally depigmented and has nodules on face and ears with gross trophic changes on the skin of legs. Several raised erythematous patches elsewhere. Those on legs are breaking and ulcerating. Had ulcers on soles of feet, Two meta-tarsals removed at operation, main en griffe both hands. Seems an intractable stationary case.

Laboratory report: SKIN 80/1, NOSE M/1, SR. 36, Hb. 55%.

Sept. 1948: Much improved. All ulcers healed. Had temporary outbreak of fresh nodules which vanished in two to three weeks. Nodules on ears and elsewhere have all unquestionably subsided. He feels better, and it is a relief to see him go about without bandages which he had for years.

Laboratory report: SKIN 40/1, NOSE M/1, SR. 29, Hb. 70%—markedly improved.

CASE 14: REG. NO. 6586: ACTIVE ADVANCED.

Sept. 1947: Admitted 1932. Has been at home at intervals for several years and indeed joined the Army. A general diffused depigmented case with multiple large coalescing nodules on back, arms, legs and some on face. Ears are grossly nodular and enlarged. His feet are swollen, and there are some ulcers on both feet. Within the last year he has got much worse.

Laboratory report: SKIN M/1, NOSE M/1, SR. 41, Hb. 60%.
R.B.C. 3,350,000, W.B.C. 3,700.

Sept. 1948: Has had still another outbreak of new nodules like those of a year ago on the surface of the skin which have remained. Diasone was stopped and then begun again at one tablet per day. Feet are grossly enlarged.

Laboratory report: SKIN M/1, NOSE M/1, SR. 70, Hb. 45%—slightly worse.
R.B.C. 3,250,000, W.B.C. 10,600.

CASE 15: REG. NO. 8043: ACTIVE ADVANCED.

Sept. 1947: Admitted 1937, female, aged 12. There are multiple patches and nodules all over body. Lately has gone down hill very much and looks active plus plus. Right eye nodular and vision impaired. R.B.C. 3,880,000.

Laboratory report: SKIN M/1, NOSE M/1, SR. 55, Hb. 60%.

Sept. 1948: Somewhat improved. Nodules have become reduced in size, and patches show less erythema. The eye remains unchanged.

Laboratory report: SKIN M/1, NOSE M/1, SR. 40, Hb. 70% slightly improved.

CASE 16: REG. NO. 4272: ACTIVE ADVANCED.

Sept. 1947: Admitted 1937, male, aged 27. Has nodules on face, arms, legs and trunk. The ears are grossly enlarged and nodular. There are multiple erythematous patches throughout. The right ulnar nerve is considerably enlarged. The left foot has talipes varus due to nerve involvement. He is anaemic. Is an active case but still able to work.

Laboratory report: SKIN M/1, NOSE M/1, SR. 60, Hb. 55%. R.B.C. 2,930,000, W.B.C. 4,400.

Sept. 1948: He has much improved and indeed looks a different man. The nodules have all gone down and the erythema has faded. The foot is straighter and the anaemia improved.

Laboratory report: SKIN M/1, NOSE M/1, SR. 60, Hb. 65% —markedly improved.
R.B.C. 3,310,000, W.B.C. 9,800.

CASE 17: REG. NO. 1886: ACTIVE ADVANCED.

Sept. 1947: Entered colony 1931, male, aged 25. Was home for three years. Returned very nodular, and has got steadily worse. Ulcers on feet with years of dressings and several operations. At present is very active case with multiple small nodules throughout and large ones on face. Main en griffe. Skin of legs much disfigured with trophic changes. Larynx is affected.

Laboratory report: SKIN M/1, NOSE M/1, SR. 57, Hb. 55%.

Sept. 1948: Not much change. Says he feels better but has still many active papules on trunk. The ulceration shows some improvement—the ulcers having dried up leaving small holes. The gross nodules have subsided somewhat.

Laboratory report: SKIN M/1, NOSE M/1, SR. 65, Hb. 68% —slightly improved.

CASE 18: REG. NO. 716: ADVANCED ACTIVE.

Sept. 1947: Came here as boy of 14 in 1930. He has diffuse depigmentation throughout body, with gross nodules on face, arms, legs, front of chest and abdomen. Has ulceration of hands and feet with gross trophic changes. He has got gradually worse and looks a hopeless and incurable case. R.B.C. 3,890,000. The left eye is nodular.

Laboratory report: SKIN M/1, NOSE M/1, SR. 26, Hb. 60%.

Sept. 1948: Improvement has taken place, the nodules have gone down, the general health improved, the ulcers on feet have improved, the eye is giving less trouble, nodules on ears have flattened out.

Laboratory report: SKIN M/1, NOSE M/1, SR. 52, Hb. 65% —slightly improved.

CASE 19: REG. NO. 2067: ACTIVE ADVANCED.

Sept. 1947: Admitted 1937, female aged 30 Has worst nodular skin in entire colony. Very gross thick raised coalescing nodules all over body. Surprisingly face has got off lightly but ears are plus plus. There are diffused thickenings on legs. R.B.C. 3,350,000.

Laboratory report: SKIN M/1, NOSE M/1, SR. 49·5, Hb. 50%.

Sept. 1948: She has considerably improved, but there is ample room for more. The nodules have been reduced throughout. She feels better and is able to work. She is less anaemic.

Laboratory report: SKIN M/1, NOSE M/1, SR. 40, Hb. 80% —markedly improved.

CASE 20: REG. NO. 4872: ADVANCED ACTIVE.

Sept. 1947: Entered colony 1941, male aged 25. Has got worse. At present has multiple nodules all over face, limbs and body. There are diffuse thickenings on legs. The ears are grossly nodular. Some anaemia—R.B.C. 3,850,000.

Laboratory report: SKIN M/1, NOSE M/1, SR. 66, Hb. 60%.

Sept. 1948: The nodules have gone down 50%, the legs remain unchanged, the ears are flattened. He feels stronger. The anaemia is less.

Laboratory report: SKIN M/1, NOSE M/1, SR. 57, Hb. 75% —markedly improved.

CASE 21 : REG. NO. 796 : ADVANCED ACTIVE.

Sept. 1947: Admitted 1929 as a boy of 13. Skin is completely depigmented, the legs show trophic changes and ulcerations. Has spent various periods extending to months in hospital. There is great disfigurement of nose—septum seems to have eroded away. Is continually getting attacks of leprotic fever.

Laboratory report: SKIN 60/1, NOSE M/1, SR. 42, Hb. 55%.
R.B.C. 3,350,000, W.B.C. 9,600.

Sept. 1948: There is some improvement. The nodules have gone down to some extent and the extensive ulceration has healed up, leaving one ulcer below great toe. The trophic changes remain, as does the anaesthesia of legs and hands.

Laboratory report: SKIN M/1, NOSE 40/1, SR. 67, Hb. 50%
—slightly improved.
R.B.C. 3,420,000, W.B.C. 5,600.

CASE 22 : REG. NO. 7853 : MODERATELY ADVANCED ACTIVE.

Sept. 1947: This is a recent admission, 1946, man aged 45. General diffused depigmentation with nodules on ears and a few throughout body and on face there are large coalescing nodules. R.B.C. 3,700,000.

Laboratory report: SKIN M/1, NOSE M/1, SR. 45, Hb. 60%.

Sept. 1948: All nodules have subsided, patches have faded. His general health is good. This is the most favourable case that was started and he has made the best response.

Laboratory report: SKIN 40/1, NOSE M/1, SR. 50, Hb. 80%
—markedly improved.

. . . . . .

We are greatly indebted to the American Mission to Lepers for supplying diasone free for these patients.

A PHARMACOLOGICAL STUDY OF THREE SULPHONES

MICHAEL SMITH

PART I—ABSORPTION, DISTRIBUTION & EXCRETION.

INTRODUCTION.

In 1908 Fromm and Wittman synthesised 4,4′ diaminodiphenylsulphone. Not until 1937, when Fourneaux and Buttle, working independently, shewed that this compound possessed a high degree of activity against a hæmolytic streptococcus, was any interest shewn in the chemotherapeutic properties of the new sulphone.

Since 1941 numerous favourable reports have been published concerning the therapeutic activity of the proprietary sulphones. Many of these reports are of a clinical nature. Ross, however (1), confines his report to blood and urine levels produced by the parenteral and oral administration of three proprietary (American) sulphones. A clinical and laboratory study of sulphones, particularly sulphetrone, was carried out during the treatment of nearly 300 patients, the majority suffering from severe lepromatous leprosy, at the British Empire Leprosy Relief Association Research Unit, Uzuakoli, S.E. Nigeria. This report will consider only the aspects of absorption, distribution and excretion. Other pharmacological aspects including the specific toxic phenomena will be reported in subsequent papers.

THE SULPHONES STUDIED.

Sulphetrone, a complex derivative of diaminodiphenylsulphone, is the subject of reports by Brownlee *et al* (2). The parent substance constitutes about one quarter of the molecule.

Diasone, the formaldehyde sulphoxylate derivative of diaminodiphenylsulphone is the subject of reports by Raiziss (3). The parent substance constitutes about one half of the molecule. Owing to currency difficulties the supply of this drug was very limited.

Diaminodiphenylsulphone is not a proprietary substance. Because of early reports of its toxicity in animals it has never been widely used as a therapeutic agent in man. With the doses required for the treatment of acute infections, severe haemolytic anaemia and methaemoglobinaemia are encountered.

Pharmacologically the most desirable sulphone is one that is least toxic, is absorbed completely from the gut, and excreted slowly in the urine. Blood and tissue levels of a therapeutic order may then be maintained on small, widely spaced doses, thus

reducing the cost of therapy, and making possible mass oral treatment with the minimum of staff.

The attempt was made to compare the three sulphones from the points of view mentioned above. To this end the faecal and urinary excretions of the three sulphones were studied at different blood levels produced by variations in the amount of drug intake. Oral and parenteral routes of administration were used.

METHODS.

1. **Determination of sulphones in blood.** The method of Bratton and Marshall as modified by Brownlee (4) was used for all three sulphones. Blood extractions were performed between 0900-1000 hours every morning, the morning dose of sulphone having been administered at 0800 hours. At the commencement of the study it was found that twice daily administration of any of the sulphones used produced reasonably steady blood levels throughout the day; the difference between minimum and maximum levels being 1mg%. For all practical purposes therefore the blood levels recorded hereafter may be considered as minimal levels.

2. **Determination of sulphones in urine.** Twenty-four hour specimens were collected, over a period of three days. Dilutions of each 24 hour sample of from 1-5 to 1-20 were found satisfactory with sulphetrone and diasone; dilutions of from 1-10 to 1-50 were necessary with diaminodiphenylsulphone. 1ml. of the diluted sample was estimated as for blood. The mean of the total three days' excretion was calculated.

3. **Determination of sulphones in stool.** As soon as possible after the passage of the specimen, the total weight of the sample was estimated. Portions of the stool were removed from various sites of the mass and placed in a tared litre beaker. The weight of sample taken was recorded, an amount approximating to 100g. was found satisfactory. This was thoroughly emulsified in c. 500ml. of $N/_1$ HCl, the whole mass was poured into a litre graduated cylinder and made up to 1000ml. A few hours were allowed for the particles to sediment, and 1ml. of the supernatent fluid was estimated as for blood. Further dilution was sometimes necessary, in this case 50ml. of the supernatent fluid were diluted 1-2, 1-4 and so on as necessary.

With stool suspension it was sometimes difficult to obtain a perfectly clear filtrate, neither centrifuging nor double filtration being effective. (In these cases attempts must not be made to clear the liquid by absorption on charcoal, since the sulphones are absorbed themselves on activated charcoal).

Visual estimation in a block comparator with a blank consisting of 1ml. of the *undiazotised* filtrate, gave better and more reliable results than other methods. A colour falling within range of from 4-9mg% for sulphetrone, 1-6mg% for diasone, and 0·4-2·0mg% for diaminodiphenylsulphone was aimed at, and dilutions of the original suspension was affected to achieve this.

The majority of the balance experiments were conducted upon patients who had been upon continuous sulphone treatment for over one month. Many observations were upon patients who had been taking a standardised dose for over six months without a break, whilst for the very high dosage levels studied, patients were used

who had been on continuous treatment for over nine months. No estimations were performed upon patients who had not been standardised upon *the dosage level under investigation* for at least 14 days.

RECOVERY OF DRUGS.

Using the techniques detailed above, the method of Brownlee (4) was found to give excellent results with all the sulphones studied. It was not found necessary to use sulphatoethyl-m-toluidine (5) as a coupling component for diaminodiphenylsulphone; thus the one method of estimation was applied to all sulphones, resulting in a considerable saving of time.

As a test of the accuracy of the method and technique of estimation, the following *recoveries* of the sulphones were obtained, measured amounts of the sulphones were added to faeces, urine and blood, (Fig. 1) estimations being made against standard tubes.

FIG. 1.

DRUG.	FÆCES.			URINE.			BLOOD.		
	Added.	*Recovered.*	*%age.*	*Added.*	*Recovered.*	*%age.*	*Added.*	*Recovered.*	*%age.*
DADPS*	0·1g.	0·11g.	110	0·1g.	0·1g.	100	10mg.	10mg.	100
DIASONE	0·5g.	0·5g.	100	0·5g.	0·48g.	96	10mg.	10mg.	100
SULPHETRONE	1·0g.	0·9g.	90	1·0g.	0·92g.	92	10mg.	10mg.	100

* Diaminodiphenylsulphone.

ABSORPTION.

Excretion of sulphones in the fæces.

Twentyfour-hour stool collections were made over a period of three days, and the mean daily excretion was calculated. Many analyses of single specimens of stool have been carried out here; they are unreliable as an indication of the *total* sulphone excreted daily in the stool, wide variations occurring between morning and evening specimens. Only the results of the three day collections are given in Fig. 2.

Fig. 2.

Excretion in Stool.

Drug.	*Daily Dose in Grammes.*	*No. of 3 day observations.*	*Mean Faecal Excretion in Grammes.*	*% Intake.*
*DADPS orally. Single administration daily.	0·1	8	0·001	1
	0·2	5	0·005	3
	0·3	13	0·008	3
	0·1	2	0·030	7·5
			Mean	4
DIASONE orally twice daily	0·3	8	0·08	27
	0·6	8	0·3	50
	0·9	6	0·4	44
	1·2	6	0·8	67
	2·7	3	0·1	41
			Mean	46
SULPHETRONE orally twice daily administration.	2	3	1·9	95
	3	8	2·4	80
	4	16	3·5	87
	5	20	4·0	80
	6	15	4·2	70
	8	15	7·7	96
			Mean	85

* Diaminodiphenylsulphone.

The restricted range of the observations with diaminodiphenylsulphone was necessitated by the fact that higher doses tend to be toxic.

Discussion.

Diaminodiphenylsulphone in the dosage employed is absorbed from the gut almost completely. In none of the analyses here has the amount of diaminodiphenylsulphone present in the faeces been greater than 10% of the daily oral intake, and it is usually much lower.

Diasone is recoverable from the faeces in amounts varying from 20-67% of the daily oral intake.

Of the daily oral intake of sulphetrone 70-100% may be recovered from the faeces. Wide variations in day to day output are found; individual stool samples containing more than the day's intake are encountered if a tendency to constipation is encountered.

It is believed that the amounts of sulphone recovered from the stool represent substantially the portion remaining unabsorbed from the gut. Excretion of sulphones via the bile and ileum do not at the most amount to more than 10% of the daily oral intake. This is shewn by the following experiment.

Parenteral Sulphetrone.

Three patients were given 4g. of sulphetrone intramuscularly, and one patient 2g. intramuscularly, as a single dose. The following table shews the faecal excretion after these doses (Fig. 3).

FIG. 3.

FÆCAL SULPHETRONE IN GRAMMES

(*Parenteral Administration*)

Patient.	Dose in Grammes.	Day 1.	Day 2.	Day 3.	TOTAL.	% age Dose Excreted.
1	4	0·2	0·08	—	0·3	7·5
2	4	0·1	0·1	0·08	0·28	7·0
3	4	0·15	0·2	0·05	0·4	10·0
4	2	0·05	0·05	—	0·1	5·0

DISTRIBUTION.

Owing to a lack of post-mortem material it was not possible to determine the concentration of the sulphones in the internal organs.

Estimation of sulphone in 1ml. of the following substances were performed: sweat, saliva, tears, lymph. Results are as shown in Fig. 4.

FIG. 4.

SUBSTANCE	Blood Level mg%	mg% Suphetrone	mg% Diasone.	mg% Diamino-diphenylsulphone.
Sweat ...	1	Trace	1·5	1·8
,, ...	2	2	—	—
,, ...	4	5	—	—
,, ...	6	4	—	—
Saliva ...	1	—	0·5	0·8
,, ...	4	2	—	—
Tears ...	1	—	Trace	Trace
,, ...	4	1	—	—
Lymph ...	1·5	—	—	3·0
,, ...	3·0	—	5·0	—
,, ...	6·0	4	—	—
Skin ...	1·0	Trace	Trace	0·9
,, ...	1·5	Trace	0·5	1·9
,, ...	4·0	4·0	—	—
,,* ...	4·0	4·0	—	—

* Macule..

Comment.

From the very limited results above we can only state that the drugs are found in the tissue fluids examined. We have not as

yet evidence of equal distribution. No evidence for the relative concentration of sulphones by the skin was found in any of 30 analyses performed. No difference in drug levels between macular and normal skin was observed when both types of skin were removed from the same patient at the same time.

Excretion.

Excretion of sulphones in the urine.

Twentyfour-hour urine collections were made over a period of three days. The mean values of these were calculated, and are shewn in Fig. 5.

Fig. 5.

Excretion in Urine.

Drug.	*Daily Dose in Grammes.*	*No. of 3-day Observations.*	*Urine Output in Grammes.*	*Proportion Total Daily Dose.*
Diaminodiphenyl-sulphone orally. Single dose daily.	0·1	24	0·08	80%
	0·2	20	0·18	90%
	0·3	20	0·23	77%
	0·4	4	0·33	83%
			Mean	
Diasone orally. Twice daily administration.	0·3	8	0·20	67%
	0·6	8	0·30	50%
	0·9	6	0·43	48%
	1·2	6	0·55	46%
			Mean	
Sulphetrone orally. Twice daily administration.	2·0	10	0·20	10%
	3·0	20	0·30	10%
	4·0	20	0·48	12%
	5·0	20	0·50	10%
	6·0	15	0·50	8%
	7·5	10	0·60	8%
	8·0	5	1·0	12·5%
	9·0	5	1·3	14·5%
	10·0	5	1·2	12%
	14·0	1	1·5	11%
			Mean	
Sulphetrone parenterally. Single dose.	2·0	1	1·9	95%
	4·0	3	3·3	83%
			Mean	

Discussion.

The assumption that the daily urinary output of sulphone is a measure of the absorption of that sulphone is open to certain objections, that (a) the drug may be degraded in the body into various non-sulphone type compounds and (b) that other channels of excretion, for example, the sweat, the bile etc., are possible.

However, for a related series of sulphones the use of the 24-hour urinary output as a measure of absorption is substantially accurate.

From the above results diaminodiphenylsulphone may be said to be extremely well absorbed, 83% of the daily oral intake being recoverable from the urine. Diasone is well absorbed, 53% of the oral intake being recoverable from the urine. Sulphetrone is poorly absorbed, only 11% of the daily oral dose being recoverable from the urine. When 4g. of sulphetrone was given intramuscularly, however, over 70% of the amount was recovered in the *first* 24 hour urine and single samples of urine were passed containing 1g. of sulphetrone per 100ml. of urine, within five hours of the administration of the drug, indicating an extremely rapid renal clearance.

BLOOD LEVELS OF THE SULPHONES.

The values given in Fig 6 represent the minimal blood levels. Observations upon sulphetrone are too numerous to detail, approximately 2,500 estimations being made with this group. The observations upon diasone are limited to a much smaller number of patients, approximately 80 observations being made. With diaminodiphenylsulphone a group of 10, rising to 50, patients has been studied for periods of from one to five months. Therapy in the majority of these cases has been continuous, and the figures given represent 230 estimations.

FIG. 6.

BLOOD LEVELS OF THE SULPHONES.

DRUG.	*Dose in Grammes.*	*Mean Minimal Blood Levels mg%.*	
Diaminodiphenylsulphone orally.	0·1	0·4	
	0·2	0·6	
	0·3	1·0	
	0·4	1·5	
Diasone orally.	0·3	0·3	
	0·6	0·8	
	0·9	1·2	
	1·2	1·5	
	2·7	4·0	
Sulphetrone orally.	2·0	1·5	
	3·0	2·0	
	4·0	3·5	
	5·0	4·0	
	6·0	4·5	
	7·0	5·0	
	8·0	5·5	
	10·0	6·5	
	14·0	7·5	
		1 hr.	*24 hr.*
Sulphetrone intramuscularly.	2·0	26	4
	4·0	40	4

Discussion.

Blood levels of 0·4 to 1·0 mg.% can be obtained with doses of diaminodiphenylsulphone up to 300 mg. daily. Approximately three times as much diasone, and about five times as much sulphetrone are needed to give comparable levels with DADPS.

The range of observations with diasone is very narrow, due to the fact that supplies of diasone were restricted owing to dollar difficulties. It should be kept in mind that these concentrations do not so far as is at present known indicate clinical solidarity, and the drugs are not compared at the same levels.

Blood level/time curves.

Fig. 7 shews the rate of fall of blood sulphone after cessation of therapy. The figures for suphetrone were compiled from five cases who had been on continuous therapy for over a year, the

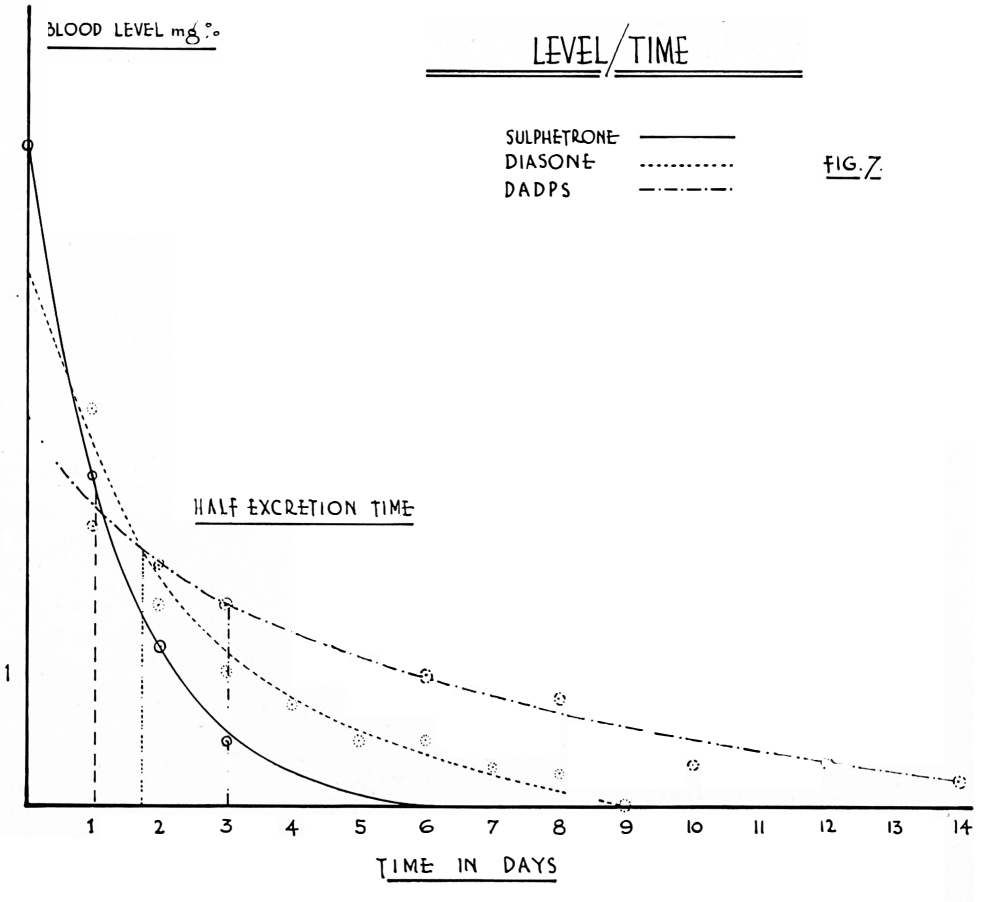

FIG. 7.

figures for diasone were from four cases who had been on continuous therapy for three months, the figures for diaminodiphenylsulphone were from ten cases on continuous treatment for six weeks.

Discussion.

The area enclosed by the curve for diaminodiphenylsulphone is much greater than that for either of the other two sulphones. The half excretion time of each of the drugs demonstrate clearly that sulphetrone is not retained in the body for any considerable period in appreciable quantities. Traces of diaminodiphenylsulphone are still detectable in blood 14 days after the cessation of a six weeks' period of administration.

FINAL DISCUSSION.

From the results presented in these studies it is apparent that diaminodiphenylsulphone meets the pharmacological criteria stated earlier in this paper better than either of the two proprietary sulphones.

Diaminodiphenylsulphone is the active radicle from which both the proprietary compounds are synthesised. Absorption from the gut is of a very high order, excretion in the urine is slow thus enabling blood levels of 1-2mg% to be maintained on oral doses of 0·3g. daily. However, the " parent " sulphone has the reputation of being too toxic a drug for use in human infections, and no reports of its therapeutic trial in leprosy are available. In the treatment of acute infections with diaminodiphenylsulphone when doses similar to those of sulphonamides are administered, it may be predicted that severe toxic effects will be manifested. When the treatment of a chronic disease such as leprosy is considered the dosage of diaminodiphenylsulphone may be adjusted (in the light of the treatment of leprosy with proprietary sulphones) to give a blood level comparable with that obtained when using the proprietary compounds, " comparable " that is in terms of chemical equivalents.

Diasone and sulphetrone are both incompletely absorbed from the gut; the absorption of diasone compares with that of some of the earlier sulphonamides, and if the oral treatment of leprosy with *proprietary* sulphones is being considered it would appear to be the drug of choice. It is suggested that parenteral administration of sulphetrone is the most suitable method of administering this compound, only 10% of the drug being recoverable from the faeces by this route.

Earlier in this paper the theoretical evidence for the breakdown

of the proprietary sulphones was considered. From the fact that the activity of both sulphones and sulphonamides is reversed by para-aminobenzoic acid a similar mode of action may be postulated. Diaminodiphenylsulphone can be isolated from the urine of patients on both diasone and sulphetrone therapy.

The importance of this lies in that if the proprietary substances are not active *per se* then a " desirable " proprietary sulphone should be degraded to a high degree, since the non-degraded compound is therapeutically inert. Further evidence may be obtained regarding this subject by a perusal of the literature upon the therapeutic trials of the proprietary sulphones. Diasone, about 50% of which is diaminodiphenylsulphone, is reported as being a fairly toxic compound—doses of the order of 1g. being advocated. If complete *in vivo* hydrolysis of the absorbed diasone occurs, about 0.25g. of diaminodiphenylsulphone is available to the body (i.e., approximately the daily dose advocated in this paper). Sulphetrone, about 30% of which is diaminodiphenylsulphone is regarded as being virtually non-toxic—doses of the order of 3g. daily being advocated. If complete hydrolysis of *the absorbed* sulphetrone occurs, about 0·1g. of diaminodiphenylsulphone is available to the body (i.e., a dose well within the toxic limits of the " parent " compound). The degree of degradation of the different sulphones is obviously a point of importance, and it is hoped to publish further work on this subject in the near future.

An aspect of great practical importance must now be considered. The treatment of leprosy with drugs of the sulphone class is a long term project, therapy of 4 years' duration and above being necessary in some severe lepromatous cases. Most countries with a leprosy problem are poor countries. It is therefore important to reduce the cost of treatment to the minimum. A proprietary sulphone poorly absorbed from the gut, rapidly excreted in the urine, and only degraded to a very small extent to the active compound would therefore not be the sulphone of choice from economic reasons alone. The sulphone of choice must be cheap as well as pharmacologically suitable: it is probable that diaminodiphenylsulphone, being a non-proprietary compound, not subject to patent restrictions, and being a by-product of several manufacturing processes will be cheap: it is certainly pharmacologically suitable.

Summary.

A study of the absorption, distribution and excretion of the sulphones used in the treatment of leprosy has been attempted.

Estimations of sulphones in the faeces shew that diaminodiphenylsulphone is extremely well absorbed from the gut, diasone is well absorbed, whilst sulphetrone is poorly absorbed.

Estimations of urinary excretion shew that diaminodiphenylsulphone is slowly but almost completely excreted, diasone is more rapidly and less completely excreted, whilst sulphetrone is very rapidly excreted, only 10-20% of the daily oral dose is recoverable from the urine, however.

The sulphones are fairly equally distributed throughout the body fluids. No evidence for the concentration of sulphones by the skin has been found.

Parenteral administration of sulphetrone is advocated, oral administration being uneconomic.

From a pharmacological point of view diaminodiphenylsulphone has great advantages in that given orally it is well absorbed, slowly excreted, and thus only a small amount is needed to establish and maintain a blood level comparable with that obtained by other sulphones.

ACKNOWLEDGMENTS.

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This work was carried out as part of the work of the BELRA Research Unit, Nigeria, director Dr. John Lowe.

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A STUDY OF LEPRA REACTIONS

G. O. Teichmann

The purpose of this study of lepra reaction occurring in the Purulia Leprosy Home has been to find out whether there are any other factors besides individual susceptibility which tend to precipitate reaction. For this reason a careful record of all reactions occurring in the Home was kept for twelve months from March 1948 to February 1949 together with the atmospheric temperatures and humidity.

Patients undergoing sulphone treatment have been excluded from this study as this group of drugs tends to precipitate reaction particularly during the first few months of use. Three patients have also been excluded as, although they had one or two lepra reactions, their bouts of fever were later found to be due to co-existent pulmonary tuberculosis and it was difficult to say how many of their reactions were leprotic. All the reactions noted below occurred in active lepromatous cases.

Environmental Conditions.

Purulia lies in the southern half of Bihar within the area in which the incidence of leprosy is high. This area includes the provinces of West Bengal, Bihar, Orissa and Madras. The climate in Bihar is much drier than in Bengal or Madras. The rainfall during the period under consideration was 63·76 inches. Two-thirds of this occurred between the last half of June and the first half of September during the rains. The winter is cold and dry but early in March the weather becomes almost suddenly intensely hot. During May the heat is intense and sudden sand storms occur followed by a rapid drop in temperature and often by rain. Purulia is nearly 700 feet above sea level, the soil is sandy and after heavy rainfall the ground soon dries.

The busiest seasons for the patients are in July when the rice seedlings are transplanted and late in November when the harvest is reaped. All patients who are able are expected to go out and do their full share of the work.

During the very hot weather in May patients are given no injections, work is reduced to a minimum and all who are physically able are allowed to visit their homes for a week or fortnight. About one hundred avail themselves of this privilege. There is another rest from injections and work at the Christmas-New Year season.

NUMBER OF PATIENTS.

The number of patients in the Purulia Leprosy Home, excluding about 30 in the cripples' wards, during the period under review was 637.

TABLE I. NO. OF PATIENTS IN HOME ACCORDING TO TYPE-GROUPS.

	Men	*Boys*	*Women*	*Girls*	*Totals*
L1 Bacillus pos.	38	12	7	6	63
L2 Bacillus pos.	148	25	101	11	285
L2 plus T.B.	5	1	—	—	6
L3	34	—	33	—	67
L now Bac. neg. ...	13	—	16	2	31
N1 Early Neural	6	[illegible]	9	[illegible]	46
N3 Terminal Neural ...	34	1	101	[illegible]	139
Active lepromatous Bac. Pos. Cases	225	38	141	17	421
Bac. Negative Cases ...	53	22	126	15	216
	278				
Active Lepromatous Cases	225	38	141	17	421
No. having Lepra reactions during year	83	14	37	6	140
% having L.R.s	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

It will be seen in Table I that the number of women patients almost equals that of the men, whereas there are twice as many boys as girls. The reason for this is that although many more men are admitted than women there is considerable difficulty in discharging the women even when symptom-free if they have the slightest deformity. The result is the presence of a large number of residual neural (N3) cases in the Home.—101 compared with only 34 amongst the men. After deducting all these N3 and early neural and lepromatous cases that have become bacillus negative there were 263 men and boys and 158 women and girls with active lepromatous disease in the Home. The percentage of these 421 lepromatous cases that developed lepra reactions during the year was 33·7%; that is approximately one third. The men, boys and girls reacted almost equally—33%, whereas the reactions amongst the women was only 26%. This is what one would expect as leprosy tends to run a milder course in women. It is, however, surprising that two-thirds of all the active lepromatous cases had no reactions at all during the twelve months although thousands of millions of bacilli were present in their bodies. Their health remained good and they were able to do a full day's work like normal individuals.

Why did some get lepra reactions and others not?

TABLE II. No. of Lepra Reactions per patient during the Year.

No. of Reactions	*Men*	*Boys*	*Women*	*Girls*	*Totals*
1	46	6	22	3	77
2	20	3	9	3	35
3	8	1	2	—	11
4	4	—	2	—	6
5	4		2	—	8
6	1	—	—	—	1
Over 7	—		—	—	

In Table II the number of lepra reactions the individual patients had is recorded. Of the 140 patients who had reactions 77 only had one reaction during the year and 112 had not more than 2 reactions.

Thus 7/9ths had two or less reactions and 2/9ths i.e. 28 cases had 3 or more reactions during the year.

Reactions varied in intensity and duration. Some had rose-red spots with only slight fever, some had high fever, some severe joints pains, nerve pains or iritis. Those who had repeated reactions tended to have them more severely though this was not always the case.

TABLE III. No. of Lepra reactions during each month of the year.

	Mar.	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.
Men ...	23	24	6	17	14	14	11	7	9	7	13	7
Boys ...	5	6	3	3	3	2	4	4	2	3	3	4
Women ...	10	4	8	5	6	6	5	4	7	1	5	3
Girls ...	—	2	1	1	1	—	1	—	2	1	—	—
Totals ...						22	2					

* During the second half of May which is very hot many patients go home for a few days. This probably accounts for the small number of reactions in May. There is however no reactionary rise in June and July showing that neither the holiday nor rest from injections did any harm.

TABLE IV. Period of year in which single reactions predominate.

Seventy-seven patients only had one reaction during the year.

Two-monthly Periods	*Men*	*Boys*	*Women*	*Girls*	*Totals*
Mar. and April	19	3	4	—	26
May and June	6	0	4	—	10
July and Aug.	9	1	8	—	18
Sept. and Oct.	4	1	3	1	9
Nov. and Dec.	4	0	3	2	9
Jan. and Feb.	4	1	0	0	5

THE EFFECT OF ATMOSPHERIC TEMPERATURE AND HUMIDITY ON LEPRA REACTION.

In Table III which shows the total number of reactions each month, and in Table IV which shows the distribution of reactions in those patients who only had one reaction during the year, it will be seen that the majority occurred during the hot dry weather between the cold weather and the rainy season.

OTHER FACTORS WHICH TEND TO ENCOURAGE LEPRA REACTIONS.

A few years ago there was a sharp rise in lepra reactions following the vaccination of a number of patients against smallpox. This year although most of the children were vaccinated and also had T.A.B. injections we had no increase in reactions.

It was noted however that other illnesses such as pneumonia and dysentery were followed by a severe reaction. Associated tuberculosis did not actually increase the liability to reaction although at first the rises in temperature were thought to be due to reaction.

Practically all the twenty-eight patients who had three or more reactions during the year had had leprosy for several years and had shown a tendency to get reactions easily from the beginning. Most could not stand more than a few cc. of Hydnocarpus oil injections without getting a reaction. We did not find that these particular patients stood large injections better as some writers have stated Some patients who had previously not been subpect to reactions after 2 or 3 years of twice-weekly large injections developed severe reactions and injections had to be reduced or stopped altogether. These patients who react to small doses have also tended to get reactions easily with soluthiazole and sulphones. They seem to have a marked sensitivity. These patients are often afraid of injections and also of doing any manual labour for fear of getting a reaction. On the other hand by judicial coaxing or urging some of them have lost this sensitivity when they have worked in the gardens. There is no doubt that regular exercise in the sun and open air is a very important factor in the treatment of leprosy, as Muir pointed out many years ago.

DISCUSSION.

Lepra reactions are an interesting and rather baffling study. Probably they are not all due to the same cause or all similar in nature. Some, as has been pointed out, are later found to be due to some associated disease and are not true lepra reactions.

Some authorities differentiate reaction in tuberculoid leprosy

from that occurring in lepromatous cases because in the former the patients are better and on the way to recovery after a reaction, whereas they are definitely worse after a bad reaction or a series of reactions in lepromatous disease. The writer, however, considers that true lepra reactions occur in both types of the disease and that they are allergic in nature. The theory that the reaction is due to a metastatic dissemination and multiplication of bacilli does not seem at all likely, as in lepromatous cases in which such reactions occur the corium already contains millions of bacilli everywhere and the addition of a few more bacilli through the blood stream would hardly cause such a flare up. Some writers claim that they have noted an increase in the number of bacilli in the rose-red nodules but such an increase must be very difficult to estimate. In the biopsy sections examined by the writer the chief thing noted was a marked increase in intercelluar exudation. The rose-red nodules seen in the majority of cases of lepra reaction are transient in nature and seldom turn into permanent firm nodules seen in nodular leprosy. They seem to have more the appearance and character of erythema nodosum of tuberculosis which is probably also an allergic reaction. The swollen painful nerves also seen in lepra reactions are not due to cellular infiltration but to an oedematous condition, and an incision of the nerve capsule often causes marked relief of pain.

The diseases which tend to precipitate a reaction—pneumonia, dysentery etc. cause a general leucocytosis, whereas wasting conditions are seldom associated with reactions.

Two very interesting cases of major tuberculoid leprosy were seen during the year. Leprosy suddenly appeared where there had been no previous sign of the disease. There was a sudden flare up with considerable fever and oedema and scattered reddish areas. Bacilli were numerous. A few months later no bacilli could be found on careful examination. These reactions seemed very similar to reactions in lepromatous cases but the body seemed to be able to react quickly to the stimulus and destroy the invader. Usually in major tuberculoid leprosy there is a rather violent response with oedema but the prognosis is good and the resultant deformity is slight. In minor tuberculoid leprosy the tissue reaction is slight and slow in catching up with the invader. The spread goes on for months or years and ultimate deformity may be considerable unless due precautions are taken. In the
of lepromatous cases unfortunately there is no tissue response and no reaction. Not all who did develop reactions were worse after them. The fact that several of these patients eventually got over the lepra reaction tendency, although in the meantime the leprosy

itself had definitely become worse, seems to point to the allergic nature of the reactions.

SUMMARY.

A study of lepra reactions was made in Purulia to find out what factors tended to cause these reactions.

It was found that the majority of reactions occurred during the hot dry season of the year.

Diseases like pneumonia and dysentery frequently precipitated reactions in susceptible patients.

It is suggested that lepra reactions are allergic in nature.

REVIEWS.

Leprosy in India, Vol. XX, No. 2. April, 1948.

What of the Children? by Dr. G. O. Teichmann. This is a useful study, and follow-up, of the fate of children, both healthy and infected, in the Purulia Leper Home in Bihar. The author summarises as follows:

"1. The history of children separated from parents with leprosy and brought up in the Healthy Home in Purulia and those who had already developed leprosy and were treated in the Purulia Colony between 1927 and 1942 is traced to the present time.

2. Although two-thirds of the children in the Healthy Home did at some period show signs of leprosy only two developed the lepromatous type and the majority are now healthy and many are married.

3. More than half of those who had lepromatous leprosy have since died and of those who remain the majority still have the disease.

4. It is suggested the children removed from infective surroundings may develop an immunity if brought up in a Healthy Home.

5. The need is stressed not only of isolating persons suffering from infective leprosy but also of removing child contacts to Healthy Homes where no further infection can take place."

Intramuscular injections of Hydnocarpus Oil and its preparations by Dr. S. N. Chatterjee. This is a timely and practical discussion on the facts that should be taken into account in the successful injection of Hydnocarpus Oil. It is still true that in many places needless pain and abscess formation are caused by heedlessness and bad technique. (It would be of great benefit to a large number of relatively inexperienced workers and to lay employees in

leprosy, if Dr. Chatterjee, with his vast experience, could make this article part of a practical series dealing with technical points in the examination and treatment of leprosy. We hope that he will consider this.—Ed.).

Leprosy in India, Vol. XX, No. 3. July, 1948.

Rehabilitation of the Physically Handicapped with reference to Leprosy, by T. N. Jagadishan. This is an interesting and sympathetic study of a problem that has been far too freqeuntly neglected. As the author states:

" It will be well to point out that those who have very large clinical experience are coming increasingly to feel that intelligent and well-planned efforts at early diagnosis (of deformity), careful treatment and management under conditions of increasing facilities can lift the burden of deformity from many a case on which that burden is now needlessly imposed."

The author's summary, which should be considered carefully by everyone responsible for the administration of leprosy, is as follows:

" Towards progress in this work of rehabilitation I would advocate:

1. The setting up of a well-equipped, well-staffed Institute of Physical and Occupational Therapy which will be at once a research and training centre. This may be part of the proposed Central Leprosy Institute of India.

2. The organizing of a Department of Welfare Work, Occupational Therapy, Community Services, etc. in every large sanatorium.

3. The establishment of Agricultural Colonies with a cottage industry bias in rural areas for the negatives and disease-arrested.

4. The establishment of After-care Colonies, like the Papworth Colony for tuberculosis patients, where light work, recreation, treatment and rest are combined.

5. The establishment of Industrial Institutes where the urban leprosy patients can find suitable work.

6. The establishment of Influential Employment Bureaux in every province with a view to re-absorption in society as far as possible of disease-arrested cases. The securing of employment for the disease-arrested and the negatives is a most diffcult task as the public continue to be afraid of infection from non infective cases. But a resolute attempt should be made to combat such prejudice and set people back in society on their own legs. The correction of deformities by physiotherapy will render this task easier.

Today we are faced with the problems of resettlement of ex-servicemen, rehabilitation of those who have suffered war-accidents, and above all the care and rehabilitation of refugees. Leprosy presents problems very similar, and it would be well to remember that the man who has been disabled in the fight against disease deserves not less sympathy than those who are disabled in war, and that the man who has to seek exile from the habitual, daily civilized cruelty of normal life deserves not less help than the refugees of the insane cruelties of the fratricide that our unfortunate country is witnessing at the present moment. Such extraordinary cruelties will become impossible if we did not throw into unregarded

corners the many sections of oppressed, ill-treated, neglected humanity in normal peace time. For our abnormal cruelties are only the acute exacerbations of our normal civilized cruelties."

A short note on experimental investigations on the optimum dose of hydnocarpus preparations at the Lady Willingdon Leprosy Sanatorium, Chingleput, S. India by Doctors Z. J. Rajah, M. Paul and R. G. Cochrane. This is a short account of an investigation to examine the optimum dose of Hydnocarpus Oil and its preparations. After various experiments by the injection of different doses by varying routes, the conclusion is drawn that the most efficient method is to combine intradermal and subcutaneous injections with a maximum combined dosage of 15 c.c. weekly.

The importance of home visits in the control of leprosy in Bombay City by Doctors N. Figueredo and S. D. Desai. The authors have studied the work carried out by Health Visitors in Bombay City over a period of 5 years. They conclude that the steps taken to follow-up patients, to ensure examination of contacts, to educate patients and relatives, and to supervise isolation have met with success and are essential in the control of leprosy.

International Journal of Leprosy, Volume 16, No. 2. April-June, 1948.

Present Status of Sulphone Therapy at Padre Bento Sanatorium, by Lauro de Souza Lima and the clinical staff of the sanatorium. This is a study of sulphone therapy in (a) advanced; (b) moderately advanced; (c) incipient lepromatous cases, with a total of nearly 850 cases. It is interesting that in a considerable series of tuberculoid cases treated with sulphone, progression of the skin lesions occurred, but no influence on the nerve lesions. In 15 cases of the uncharacteristic type, 8 have completely cleared up and three have been converted to the tuberculoid form. At the Lapa Dispensary 130 cases with uncharacteristic lesions received sulphone treatment for eight months. During that period none of the cases have become lepromatous and some have shown partial improvement. Bacteriological and histological findings are also discussed in detail. Dr. de Souza Lima's discussion and summary is as follows:—

DISCUSSION.

"The results of sulphone treatment of which an over-all picture has been presented, never before recorded with other drugs, were obtained without any accident of importance, attesting to perfect tolerance for this medication in all forms of the disease and at all ages. The dosage should be raised to the maximum whenever there is no contraindication. Visceral involvement is no contraindication; on the contrary it is much benefited by this therapy.

Practically speaking, there are no appreciable differences between the results obtained with the oral and the intravenous routes of administration, when they are used exclusively. Our experience indicates that there is an evident superiority in the combination of the two routes, concomitantly or in alternating series. Nevertheless, there are cases in which intravenous injections are definitely preferred. These are: (a) all acute cases, especially those with the so-called leprotic ocular reactions, in which intensification of the intravenous sulphone therapy is decisive and quickly arrests the process; (b) cases of acute eruptions of erythema nodosum or multiforme types, without marked fever; and (c) most important, certain cases of erythema nodosum provoked by the oral administration of the sulphones, which have the special character of being accompanied by ostealgias, arthralgias and intense neuritis; these cases subside when the intravenous administration is substituted for the oral.

In our intensive employment of sulphone therapy for more than four years we have not observed any accident of major importance. The incidents and accidents which would suggest discontinuing the employment of these drugs were predominantly of temporary nature provided, of course, the treatment was correctly oriented. In this connection three kinds of phenomena were observed: (1) Phenomena of toxicity due to the medicament, especially anaemia, without any serious consequences when the proper measures to correct them are taken. (2) Phenomena of intolerance on the part of the patient, such as nausea, vomiting, intestinal disturbances, which might be serious should the treatment be unwisely continued; also certain forms of dermatitis, among them one of special aspect, tricophytoid, and all of them without any real importance. (3) Specific phenomena due to leprosy itself, represented by acute eruptions of erythema nodosum or erythema multiforme, which when not accompanied by marked fever do not indicate a suspension of treatment; and the condition called " pseudoexacerbation " of the disease for which increase of the daily dosage is indicated.

SUMMARY.

Terminating our summary exposition of the results of sulphone therapy at the Sanatorio Padre Bento, we can state in conclusion that:

(1) Sulphone therapy is not yet the ideal treatment we have been wishing for for the treatment of leprosy, but in view of the results so far obtained in a large number of cases over a long period of time it constitutes a really active and useful treatment, the only one in the history of leprosy.

(2) It is highly desirable that its benefits be extended to all segregated patients, and to the dispensaries for treatment of early cases, even to those which are non-infectious, as a possibility—at the moment—of approaching with success the problem of the prophylaxis of leprosy."

A Comparison of Sulphone and Hydnocarpus Therapy of Leprosy, by Dr. R. G. Cochrane. In this study the author has specifically excluded neuro-macular or neuro-anaesthetic cases. In early lepromatous cases under intensive treatment with hydnocarpus preparations 50 per cent of cases become bacteriologically negative in an average period of 94 weeks. He concludes:—

" So far as the Indian race is concerned, the sulphone remedies are at present indicated only in the following types of cases:—

(1) Advanced lepromatous cases, especially those with nasal and laryngeal symptoms.

(2) Cases which have not responded to properly administered hydnocarpus therapy.

(3) Cases which have relapsed.

Our better results with hydnocarpus remedies are explained on two grounds. First, the Indian racial group with which we usually work responds better to the hydnocarpus therapy than Europeans. This is demonstrated in our generally poor results with hydnocarpus in the Anglo-Indian (Eurasian) group. Second, our insistence on intensive intradermal medication."

Comparative Study of Chaulmoogra Oil in high doses and Promin in the Treatment of Leprosy, by Dr. Salomon Schujman. In this brief paper the author gives a precis of his results:—

" For comparative appraisal of the results obtained with each medicament, we have studied in our patients the clinical, bacteriological and histological evolution shown by similar lesions.

It would be premature to say, after an investigation lasting only a year and one-half, which of the two drugs is the more active; observation of the future evolution of these cases is necessary. We can, however, affirm that they are both efficient, and emphasize especially the following facts:

1. Both the sulphone used and chaulmoogra in the large doses given have an evident therapeutic activity in lepromatous cases.

2. Both drugs, administered as described, give within the same period of time similar favourable results.

3. Both drugs benefit not only the cutaneous lesions, causing levelling of the tubercles and reabsorption of the nodules, but also the lesions of the mucosa, with improvement of rhinitis and healing of erosions and ulcerations.

4. We have noted in both groups of cases that the clinical improvement is accompanied by the same favourable bacteriological alteration (fragmentation and diminution of the bacilli) and histopathological changes (gross cellular reticulation, diminution of the infiltrate, and sclerosis).

5. Although none of the patients of either group discontinued treatment, tolerance has been inferior in those undergoing chaulmoogra treatment because of pain and aseptic abcesses experienced by some of them."

CONCLUSION.

" Because of the similarity of the results obtained with these drugs up to the present moment of observation—a more prolonged observation should establish whether one of the two is more effective—it is concluded that all investigations designed to increase the tolerance to and therapeutic activity of both the sulphones and chaulmoogra oil or its derivatives should be stimulated.'

Bone Changes in Leprosy under Sulphone Therapy, by Drs. P. T. Erickson and F. A. Johansen. This study of bone leprosy should be studied in full as it is a subject to which far too little attention has been paid It is a study of 82 patients showing by X-Ray leprotic involvement of osseus tissue. While the authors suggest that the sulphone treatment of these cases has had a predominant effect in the arrest of bone changes, it should be noted that the patients also received vitamins, iron, liver and calcium preparations. The discussion and conclusions by the authors are as follows:—

DISCUSSION.

"One of the most recent and extensive clinical and roentgenologic reviews of bone changes in leprosy is that by Faget and Mayoral. In an exhaustive study of 505 cases at the National Leprosarium these investigators, in addition to confirming the existence of bone lesions in leprosy previously described by others, made it clear that certain of them correspond to certain categories of the disease.

It is the opinion now, for instance, that lepromatous leprosy, if relatively free from neural involvement, is usually free from bone lesions except those possibly due to the direct action of M. leprae. Such lesions are cysts and osteomyelitis. Enlarged nutrient foramina due to vascular disturbances also occur, as do osteomyelitis and periostitis from secondary infections. The most intense and important bone changes occur in the pure neural type, where the degenerative effects from nerve involvement cause secondary bone absorption of neurotrophic nature. In mixed cases are seen bone changes common to both the lepromatous and neural types.

It appears, then, that the important consideration is the nerve lesion, and that in order to arrest bone changes—except in the rather rare, probably true lepromatous involvement—the leprous nerve process must be aborted. Existing permanent injury and degeneration of nerves cannot be corrected, and bone changes may occur long after the time of that injury.

Although the figures given are not significant because of the small numbers of patients concerned, they indicate that sulphone treatment probably produces a restraint on further progression of atrophic bone absorption. The degree of this restraint depends in a large measure on the extent of neural involvement prior to treatment. If the nerve changes are marked, bone changes are liable to continue; if involvement of the nerves is slight or early, arrest of the process in the bones is probable. Early treatment is therefore of primary importance with a view to preventing extensive neural involvement and secondary bone changes.

Bone cysts and osteitis or osteomyelitis, presumably of leprotic origin, have been noted to heal more rapidly under sulphone therapy than that observed in our experience as due to spontaneous healing. The same can be said for necrosis of bone secondary to infected trophic ulcers. Two almost identical cases of local rarefying osteitis of the head of the astragalus, appearing shortly after inception of sulphone treatment, later healed within a relatively short time. These cases are not included in the comparison groups because of lack of five-year follow-up studies. Improvement in bone texture or rarefaction and in diffuse rarefying osteitis, also, does take place under sulphone therapy.

Another bit of evidence that sulphone treatment has been beneficial is indicated by the proportion of true lepromatous cases found in each group. Group II contains a slightly higher percentage of such cases than Group I. Because of this factor of selection, less bone involvement and less increase in bone changes would be expected in Group II than in Group I providing sulphone treatment has no effect. The results obtained are the contrary, and in favour of sulphone treatment.

Spontaneous arrest of bone changes, such as atrophic absorption and spontaneous healing of cysts, undoubtedly occurs, as does spontaneous

regression in skin lesions. To what extent such a process has occurred in this study it is difficult to determine. The fact, however that the shorter-treatment group did not do as well as the group treated for more than five years suggests that the lack of retrogression of bone changes in this group was not entirely due to spontaneous arrest.

To give a definite answer as to the value of the sulphones in bone lesions of leprosy, a more prolonged study of a larger group of patients is necessary. Any follow-up period of less than ten years is considered insufficient for determining the true probability and degree of prevention or arrest.

CONCLUSIONS.

Observations of bone changes in leprosy over a five-year period in a group of patients treated adequately with sulphone drugs indicates that lesions of bones presumably due to the direct action of M. leprae, such as cysts, heal; and that a restraint on further progression of atrophic bone absorption, secondary to neural involvement, probably occurs.

Where extensive neural involvement is present prior to treatment, secondary bone changes are liable to increase in severity.

The apparent relatively rapid healing of bone cysts under sulphone treatment suggests that they may be true lepromata of bone.

Studies of bone changes during treatment of leprosy must of necessity be of long duration because of the usual slow evolution of such lesions, and the slow response of most leprous lesions to treatment.

The prevention of bone changes in leprosy through early treatment with sulphones is an apparent possibility.

Further study of bone changes during sulphone therapy, in a larger group of patients over a longer period of time, correlated with accurate observations on nerve lesions, is recommended as necessary before final conclusions can be drawn."

The Present Status of the Sulphones in Therapy, by Drs. A. E. Sharp and E. H. Payne. This article is a general study of sulphone therapy ending with a plea for the complete avoidance of any control of these drugs. [The authors apparently fail to realise that the indiscriminate use of anti-leprosy drugs by patients and physicians with inadequate knowledge will almost certainly (a) drive the disease underground and (b) lead to a spread of infection by cases which, although clinically improved, may still be highly positive.—Ed.]