

TWO-AND-A-HALF YEARS' EXPERIMENTAL WORK ON THE SULPHONE GROUP OF DRUGS

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The sulphone group of drugs, the chief of which is diamino-diphenyl-sulphone, was first used in 1937 in experimental streptococcal infections in mice. The compound itself, diamino-diphenyl-sulphone, was reported in 1908 by Fromm and Whitmann, but it was not until 1941 that any derivative was used in the treatment of infections with acid fast bacilli. Feldman, Hinshaw *et al* (1941) reported on successful treatment of experimental tuberculosis with promin. It was natural that as soon as this substance was discovered to have an action on the M. tuberculosis, sooner or later it would be used in leprosy. The first persons to undertake work with promin in leprosy were Faget, Pogge, Johansen *et al* (1943) who first reported the successful treatment of leprosy by this drug. Since that date a great deal of work has been done on the sulphone derivatives. For a complete bibliography readers are referred to a paper by Sharp and Payne recently read at the Fifth International Leprosy Congress, Havana (1948).

Work on the sulphone derivatives was started in the Lady Willingdon Leprosy Sanatorium in 1945, when the first patients were placed on promin. Later diasone became available. It was, however, realised from the start that even though the sulphone derivatives were effective in leprosy their method of administration and their price constituted the most serious drawbacks to their use in the treatment of large numbers of persons suffering from leprosy in India, China and Africa. The senior author, when in the United Kingdom, visited the biological experimental laboratories of the

Imperial Chemical Industries at Wilmslow and discussed with workers the possibility of using diamino-diphenyl-sulphone as a therapeutic agent in leprosy. Owing to its insolubility and its known relative toxicity, a 15% suspension in arachis oil was first prepared. This was injected intra-dermally. Even though at that time the methods for skin estimation were crude and there were several fallacies, it was considered as a result of this work that the skin tissues were one of the sites in which the sulphones were deposited. Hence the intra-dermal method was abandoned and the sub-cutaneous method of injection adopted. This article is an attempt to summarise the experimental work, with diasone and sulphetrone by mouth, and the injectable sulphones—diamino-diphenyl-sulphone and sulphetrone—by sub-cutaneous injection. Facts will be given which will strongly support the plea that not only is this latter method practicable, but that a very much smaller dosage of the remedy is necessary and thereby the price may be reduced to an extent which brings the sulphone preparations within the reach of the masses.

The cases placed on diasone and sulphetrone will be first reviewed and then a brief description of those cases which have been receiving sulphone by injection and sulphetrone by injection for over four months will be given. Finally, comparative tables will be included showing the relative efficacy of the drug by mouth and by injection with a comparison of dosages and length of time to effect bacteriologic improvement. In order that there might be a method by which results with the various sulphones may be compared with cases given hydnocarpus oil, an arbitrary standard has been set, which is as follows:—16 smears are taken from each patient and as reported by one of us the bacteriologic index is worked out.* In this way a rough estimation not only of the efficacy of the drugs can be obtained, but a comparison of these drugs with hydnocarpus oil therapy reached.

CASES GIVEN PROMIN AND DIASONE

CASE NO. 1. ANGLO-INDIAN, MALE, AGE 43.

This patient has had a history of leprosy since 1917 and illustrates the usual experience in such cases of having been

**Bacteriologic index.* To estimate the bacteriologic index add up the total number of positive smears and divide by sixteen. The bacteriologic index will thus vary from 6.00 to 0, the former being from a case where all smears are 6 plus and the latter from the case which shows no bacilli in any of the smears taken. (e.g. If the plus values of all the sixteen smears added up gives a total of 64, then the bacteriologic index would be $64 \div 16 = 4$.) The index in this paper is taken to the nearest digit. Decimal places are considered of little value except when the index falls below 0.5 when the figure is indicated by 0.5—.

admitted into several leprosy hospitals. He applied to the Lady Willingdon Leprosy Sanatorium for admission in 1929. He left the Institution in 1930 without a certificate, returned in 1935, and has been there ever since. The history of the disease prior to sulphone therapy showed periods of slight bacteriological improvement followed by intervals of deterioration. As so often happens in this racial group, the intervals of deterioration increased until it could be said that he had reached the stage when hydnocarpus remedies no longer benefitted him. The bacteriologic index prior to commencing promin was 2.

Promin therapy:

From 6.11.45 to 7.11.46 he was given promin, 5 c.c. per day intravenously, except Sundays. His general condition deteriorated and he complained of much weakness, although his haemopoietic system did not appear to suffer much damage. The blood examinations remained fairly constant at 3.98 million red cells and 11.2 grammes haemoglobin. On promin, clinical and bacteriological improvement was not significant but nasal blockage was much relieved. In November 1946, when promin was stopped, the bacteriologic index was still 2.*

Diasone therapy:

In November 1946 the patient was placed on diasone, and at this time, he was a moderately advanced leprosy case (L2) with diffuse lepromatous lesions, thickened ear lobes and infiltrated eyebrows with marked infiltrations on the cheeks and chin. Apart from the ears there was no definite nodulation. The patient was given 3 capsules a day up to August 1947 when he received 4 capsules a day. Within three months the patient began to show clinical improvement and his lesions have now considerably subsided, but bacteriologically there has been little improvement. The bacteriologic index for the months of November, December and January 1948 remained at 1. During this period regular estimations of the blood level were made and the average percentage diphenyl-sulphone detected was 2 mgm%. It is assumed that diasone is broken down to the parent substance, diamino-diphenyl-sulphone. In the discussion on the administration of sulphones by mouth reference will be made to the fact that diamino-diphenyl-sulphone appears to be deposited in the skin. The skin level in this case, however, even after one year's medication, did not rise over 1 mgm% of skin tissue. The clinical feature was a marked improvement in the patient's nasal condition. The patient said that he now could breathe freely and on examination all crusts had separated. These previously were troublesome. Since 12.1.48

the patient's progress has been slow and during the past four months, as judged by his clinical appearance and the bacteriologic index, little progress has been made. The bacteriologic index on 20.10.48 was still 1.

Up to this date he has had 1,040 grammes of diasone.

CASE NO. 2. INDIAN, MALE, AGE 24.

Admitted to the Lady Willingdon Leprosy Sanatorium on 11.1.43 as a moderately advanced lepromatous case (L2). Bacteriologic index on admission was 2. He was placed on routine hydnocarpus medication reaching a maximum dose of 5 c.c. ethyl esters intradermally with a varying dose of oil. Hydnocarpus oil was discontinued sub-cutaneously as the patient tended to go into reaction. After two years there was some clinical improvement but on the whole the bacteriological condition had deteriorated and his index was 3.

Promin therapy:

Between 11.3.46 and 7.11.46 the patient was given promin, 1 ampoule every day (5 c.c.) except Sunday. During this period he showed some clinical but no appreciable bacteriological improvement. On 7.11.46 his index was 3. As has been reported by other workers there was improvement of his nasal lesions clinically, all crusts having separated and ulcers healed.

Diasone therapy:

On 7.11.46 diasone therapy commenced. The patient was given 3 capsules a day up to August 1947 when he received 4 capsules a day. During diasone treatment to date there has been clinical improvement which, though not striking, was definite and there was considerable subsidence of the lesions. Bacteriologically, however, there was deterioration, although the bacilli were more granular. In December 1947 the index remained at 3 as also on January 6th 1948. Since that date the patient has shown little improvement clinically and bacteriologically, the index in October 1948 being still 3.

The total amount of diasone given to the end of October 1948 was 766 grammes.

CASE NO. 3. ANGLO-INDIAN, MALE, AGE 23.

This patient was admitted into the Lady Willingdon Leprosy Sanatorium on 17.8.42 as a moderately advanced lepromatous case (L2). Clinically he appeared to be worse than the bacteriologic index would indicate. His index on admission was 1. The

patient was under treatment for four years with hydnocarpus remedies. The highest weekly dose reached was 3 c.c. hydnocarpus oil sub-cutaneously and 4 c.c. ethyl esters intra-dermally. During the whole of this period the patient's condition gradually deteriorated as is so often the case in this racial group. In August 1946 the index was 3.

Diasone therapy:

The patient commenced diasone in August 1946 and was given 3 capsules a day up to August 1947 when he received 4 capsules a day. The bacteriologic index during the months of September 1947 to January 1948 remained at 3. The index showed no improvement and the last index was still 3 (October 1948). This patient showed no reduction in his red cells and the haemoglobin content of the erythrocytes remained constant. While he showed in the early stages signs of lepra reaction and his clinical condition improved extremely slowly, an outstanding feature was that his nose and throat symptoms, which showed themselves in blockage and ulceration combined with a husky voice, improved very markedly.

The total amount of diasone taken to the end of October 1948 was 885 grammes.

CASE NO. 4. INDIAN, MALE, AGE 23.

This patient was admitted to the Lady Willingdon Leprosy Sanatorium on 22.6.44. He had moderately advanced lepromatous leprosy with nodules and infiltrations especially on the buttocks, upper and lower extremities and ears, with considerable nasal blockage (L2). Bacteriologic index on admission was 2. After 2 years and 11 months of hydnocarpus treatment with a maximum weekly dose of 5 c.c. hydnocarpus oil sub-cutaneously and 5 c.c. ethyl esters intradermally, the patient showed clinical and bacteriological deterioration. The index in May 1947 was 3.

Diasone therapy:

The patient was placed on diasone in June 1947 and was given 3 capsules a day until October 1947, when 4 capsules were administered. In two months the patient showed slight clinical improvement but definite improvement of his nasal condition. The bacteriologic state, however, in December 1947 had deteriorated to 4 and on 6.1.48 it was still 4. This patient unfortunately left the Sanatorium without permission in September 1947 and has not returned.

CASE NO. 5. INDIAN, MALE, AGE 28.

This was a case of moderately advanced lepromatous leprosy showing extensive infiltrated lesions. He was admitted into the Lady Willingdon Leprosy Sanatorium on 1.3.44 and had hydnocarpus treatment for 2 years and 5 months. There was temporary improvement, but subsequently he showed deterioration both clinically and bacteriologically.

Diasone therapy:

The patient was placed on diasone on 19.8.47 starting with 3 capsules a day. Between 19.8.47 and 15.4.48 he showed mild lepra reaction but this was not severe enough to necessitate suspension of treatment, nor did it incommode the patient. The patient has shown considerable clinical improvement. Lesions have to a great extent subsided and nasal symptoms have been alleviated. At the commencement of diasone therapy the bacteriologic index was 2. Thirteen months later he showed considerable improvement and the bacteriologic index was 1. In October 1947 he left the Institution without permission and returned in April 1948. His clinical condition remained the same and his bacteriologic index was still 1. He re-started diasone therapy with 4 tablets a day on 1st July 1948 and his clinical condition showed no appreciable improvement, but by October 1948 the bacteriologic index had slightly deteriorated, 2. His blood picture remained satisfactory throughout.

Up to October 1947, when he left the Institution, the patient received 431 grammes of diasone; since July 1948 he has received 71 grammes.

CASE NO. 6. INDIAN, MALE, AGE 23.

This patient was admitted to the Lady Willingdon Leprosy Sanatorium on 24.3.33, when 9 years of age, as an early macular case negative to standard methods of examination, and classified as incipient (pre-leproma). He was discharged in November 1933 and re-admitted on 11.9.36 as a lepromatous case. He remained in the Sanatorium until 24.10.41 and was discharged as non-infective. He was re-admitted on 1.4.42 with early macular lepromatous leprosy. In April 1942 his bacteriologic index was 1. The patient received routine treatment for almost four years, reaching a maximum weekly dose of 10 c.c. hydnocarpus oil sub-cutaneously and 6½ c.c. ethyl esters intradermally. At the end of this period the index was still 1 and he showed no significant clinical improvement.

Diasone therapy:

In August 1946 he was placed on diasone, 3 capsules a day, and in August 1947 he was given 4 capsules a day. The red cell count and the haemoglobin index remained fairly constant. The bacteriologic index remained at approximately 1 throughout this period. Since January 1948 improvement in the patient's clinical condition has been steady and the bacteriologic index has greatly improved and is now 0.5—. The present dosage is 4 tablets a day.

The total amount of diasone taken to the end of October 1948 was 875 grammes.

CASE NO. 7. INDIAN, MALE, AGE 24.

This patient was admitted into the Lady Willingdon Leprosy Sanatorium in July 1939. His bacteriologic index was then 2. Within a period of 2 years and 2 months he became negative and took his discharge before he qualified for a non-infective certificate. Four years later (1945) he was re-admitted as a moderately advanced infiltrated lepromatous case. His bacteriologic index was 2. He received routine treatment with a weekly dose of 6½ c.c. esters with no hydnocarpus oil as he was unable to tolerate this. Between August 1945 and August 1946 he showed no clinical and no bacteriological improvement. The index in August 1946 was still 2.

Diasone therapy:

Diasone was commenced in August 1946, 3 tablets a day, and in August 1947 4 tablets a day were given. By January 1948 he showed perceptible clinical improvement but his bacteriological improvement was not commensurate with this and the index had only been reduced to 1. Between January 1948 and April 1948 he passed through a stage of reaction when he exhibited rose spot nodules on the thighs and ears. The reaction was mild and did not last long. His bacteriologic index, however, deteriorated in April 1948 to 2. From April 1948 to October 1948 he showed a greater amount of clinical improvement and his bacteriological improvement was steady but slow, the index being 1.

Up to October 1948, 750 grammes had been taken.

CASE NO. 8. INDIAN, MALE, AGE 21.

This patient was admitted to the Lady Willingdon Leprosy Sanatorium in July 1941 and placed on routine treatment. He was discharged as a quiescent case (negative smears at monthly intervals for six months) 2 years and 2 months later. During this period the maximum weekly dosage was 5 c.c. hydnocarpus oil sub-cutaneously and 5 c.c. ethyl esters intra-dermally. The

patient returned only six months later having a relapse and clinically was a macular lepromatous case. The bacteriologic index then was 1. He was unable to take more than $3\frac{1}{2}$ c.c. hydnocarpus oil sub-cutaneously and so was placed on intradermal injections and reached 5 c.c. Then he quickly became worse and by November 1946, when he was placed on diasone, he was a very advanced lepromatous case. His bacteriologic index was 5.

Diasone therapy:

From November 1946 to September 1947 the patient received 3 tablets of diasone a day. In July 1947 he showed signs of reaction which were severe enough to necessitate the tablets being suspended for a week. The patient was then placed on 4 tablets of diasone a day. Nasal lesions showed marked improvement. Clinical improvement was very slow but gradual, while bacteriologically he showed little appreciable improvement. The index in January 1948 was 4. During 1948 clinical and bacteriological improvement continued to be very slow and while he only showed signs of slight reaction, these signs had not altogether subsided by September 1948, and by October 1948 the bacteriologic index had only been reduced to 3.

The total amount of diasone taken up to October 1948 was 766 grammes.

CASE NO. 9. INDIAN, MALE, AGE 27.

This patient was admitted to the Lady Willingdon Leprosy Sanatorium in March 1946 as an early lepromatous case with a bacteriologic index of 1. He remained in the Institution and nine months later showed no bacteriological or clinical improvement, and had been in hospital for reaction in December 1946.

Diasone therapy:

He was placed on diasone in December 1946 and was given 3 tablets a day until August 1947, when he was given 4. During the first six months of treatment he showed periodic attacks of lepra reaction which resulted in deterioration of the clinical condition, although the nasal discomfiture was relieved. In December 1946 the bacteriologic index was 1. By December 1947 his deterioration was shown by a rise in the index to 3. While there has been since this date some clinical improvement, the bacteriologic index has shown no marked change and is still 2. During January 1948 there was further reaction as shown by rose spot nodules accompanied by ulnar neuritis.

Up to the end of October 1948 approximately 654 grammes of diasone were taken.

CASE NO. 10. INDIAN, MALE, AGE 23.

This patient was admitted in April 1939 with a bacteriological index of 2. After 3 years and 5 months on a maximum weekly dose of 5 c.c. hydnocarpus oil sub-cutaneously and 5 c.c. ethyl esters intradermally, he was discharged as a non-infective case (three negatives at monthly intervals), but two years later he was re-admitted. His condition had shown very marked deterioration. He was placed on routine treatment, had frequent attacks of lepra reaction and showed no improvement either clinically or bacteriologically. In November 1946 the bacteriologic index was 3.

Diasone therapy:

He was put on diasone on 3.11.46 starting with 3 capsules a day. During the first three months of treatment he showed signs of reaction and in February 1947 he was in hospital with fever and rose spot nodules and inguinal adenitis. He remained in hospital for three weeks, during which time diasone was suspended and he did not start this drug again until the last week of May. From May 1947 to September 1947 he showed steady but slow clinical improvement. The nasal blockage was noticeably relieved. By January 1948 there was considerable clinical improvement, particularly with regard to nasal blockage, and there was some bacteriological improvement in that the index was now 2. During 1948 however, the patient began to show more rapid clinical improvement. There was marked subsidence of lesions, particularly on the face, and the nasal condition was largely relieved. As is usual in these cases, however, the bacteriological improvement was not commensurate with the clinical improvement and remained at 2.

Up to October 1948 he received 649 grammes of diasone.

CASE NO. 11. ANGLO-INDIAN, MALE, AGE 26.

This patient has had leprosy since he was 12 years of age and was admitted into the Lady Willingdon Leprosy Sanatorium in July 1934 when he only had one erythematous lesion on the right cheek. He was discharged within a year and was re-admitted in January 1936 for a trophic ulcer. Clinically he was found to be negative. He was in hospital approximately six months and then discharged. Three months later he was again admitted. This time the lesions were bacteriologically positive and he was a lepromatous case. He however responded remarkably well to hydnocarpus treatment and was discharged with negative smears after four months. He was out of the Institution for nearly two years and returned in July 1941 as a moderately early lepromatous case.

His bacteriologic index then was 1. He was placed on routine treatment and reached a maximum weekly dose of 9 c.c. divided sub-cutaneously and intradermally. Seven months later he showed negative smears and was discharged in July 1942 as a quiescent case. He was away for a period of 4 years and 5 months and returned in December 1946 with a serious relapse. He was a moderately advanced lepromatous case (L2) showing infiltrations and nodules. His bacteriologic index was 3. The patient now, as so often is the case, was extremely difficult to treat and only reached a dosage of $6\frac{1}{2}$ c.c. divided equally between the sub-cutaneous and intradermal routes. By May 1947, he had shown no improvement, his index being 3.

Diasone therapy :

In May 1947 he was placed on diasone, starting with 3 capsules a day. For three months the patient showed no improvement. In July 1947 he developed severe lepra reaction with all the usual signs and, curiously enough, he showed signs of gynaeconomastia for the first time. He was put into hospital, his reaction was treated and he was discharged from hospital at the end of the month. In August 1947 he re-started diasone and was placed on 4 capsules a day, and in September 1948 on 5 capsules a day. Up to January 1948 he showed some clinical improvement in that his reaction condition had subsided to a great extent, although from time to time he showed signs of mild reaction. In January 1948 the bacteriologic index was 3. Since that date the reaction phase has passed and he is beginning to show more steady improvement. His index in October 1948 was 2. His blood picture throughout has been satisfactory.

Up to the time of his severe reaction he only had 82 grammes of diasone. From August 1947 to the end of October 1948 he had 515 grammes in addition.

CASE NO. 12. ANGLO-INDIAN, MALE, AGE 42.

This case was an extremely interesting one in that he was first admitted to the Lady Willingdon Leprosy Sanatorium on 17.4.37 and placed on large doses of hydnocarpus oil; maximum weekly dose 20 c.c. hydnocarpus oil sub-cutaneously and 5 c.c. ethyl esters intradermally. He took his discharge before his smears were completely negative on 10.11.39. His bacteriologic index on admission was 4 and on discharge, except for a few broken and granular bacilli in the right and left ears, he was negative. In December 1944, five years later, he stated that he first noticed a relapse, and by August 1946 when he was re-admitted to the

Institution he was a very advanced lepromatous case with numerous nodules which had broken down and ulcerated. He had severe throat lesions.

Diasone therapy:

He was placed on diasone from the date of re-admission (August 1946), 3 capsules a day up to July 1947, 4 capsules a day up to December 1947 and from then up to April 1948, 5 tablets a day. From May 1948 to date he has had 6 tablets a day. This patient, as so frequently is the case in these advanced nodular lepromas, showed steady improvement, particularly with reference to his nasal condition which was much alleviated within six months. The improvement of his throat condition was still more marked. In August 1946 there was extensive lepromatous granulation tissue in the larynx; three months later infiltrations had subsided; nine months later all active signs of the disease had disappeared from this region. While his nodules subsided and all the ulcers healed, his bacteriological condition improved comparatively slowly. In August 1946 the index was 3 and by January 1948 it had only been reduced to 2. During 1948 the clinical condition continued slowly to subside, and by October 1948 the index was 1. This, interestingly enough, is the most dramatic case, and it is of significance to note that it again was a nodular lepromatous case.

Up to October 1948 he had a total of 1025 grammes.

CASE NO. 13. INDIAN, MALE, AGE 23.

This patient was admitted in September 1939 with macular lepromatous leprosy, moderately early, bacteriological index 1. Although this was an early lepromatous case, over a period of seven years the patient did not become negative on hydnocarpus treatment.

Diasone therapy:

In August 1946 he was placed on 3 tablets of diasone a day and from May 1947, 4. The bacteriologic index on commencement of diasone was 2. For six months the clinical condition showed only slight improvement. One year later fresh lesions appeared in the form of sub-cutaneous nodules but no other signs of reaction were observable. By January 1948 the index was 1. During 1948 his clinical condition showed little or no improvement and his bacteriologic index had deteriorated and is now 2 (October 1948).

Up to August 1947 he had approximately 300 grammes; from August 1947 to October 1948 he had a further 530 grammes.

(NOTE.—There has not been a single negative in adults on diasone in the 2½ years.)

CHILDREN

CASE NO. 14. INDIAN, MALE, AGE 16.

This patient was admitted to the Lady Willingdon Leprosy Sanatorium in October 1942. On admission his bacteriological index was 2. Three years and ten months later the index was still 2. The maximum dosages of hydnocarpus oil were $3\frac{1}{2}$ c.c. hydnocarpus oil sub-cutaneously and $3\frac{1}{2}$ c.c. ethyl esters intradermally. By August 1946 the patient showed some clinical improvement but the bacteriologic index still remained at 2.

Diasone therapy:

The patient was placed on diasone in September 1946 and given 2 capsules a day; after August 1947 he was given 3 capsules a day. In January 1947 he showed signs of reaction of sufficient severity to discontinue treatment for three weeks. In January 1948 there was some clinical improvement but no bacteriological improvement.

Unfortunately the boy absconded on 21.1.48.

CASE NO. 15. INDIAN, MALE, AGE 16 (LI).

This patient was admitted to the Lady Willingdon Leprosy Sanatorium in September 1945. He was given hydnocarpus therapy, the maximum dose reached being 7 c.c. divided approximately equally between the intradermal and sub-cutaneous routes. On admission the bacteriologic index was 2. Ten months later, in July 1946, the index was 1. While it cannot be said that this case would not have become negative on intensive intradermal treatment, the patient was a sufficiently advanced case to place on diasone, particularly as he complained of nasal blockage.

Diasone therapy:

The patient was placed on diasone on 12.9.46, commencing with 2 tablets a day until August 1947 when he was given 3 tablets a day. In November 1946 the case showed considerable clinical and some bacteriological improvement (index 1). In January 1948 the index was still 1. By September 1948 the patient's condition had continued to improve and his bacteriologic index had become nil, indicating that he was now negative. In October 1948 smears showed a few fragmented bacilli in the left ear and forehead, the index being 0.5—. This, however, may not be significant.

Up to the end of October 1948 the patient had taken 598 grammes of diasone.

CASE NO. 16. INDIAN, MALE, AGE 16.

This case was admitted in March 1944 as a moderately early lepromatous case with diffuse lesions on face, back, extremities, etc. On admission his index was 2. He was placed on the usual routine treatment, reaching a maximum dose of 9 c.c. approximately equally divided between the sub-cutaneous and intradermal routes. He was chosen because he was an early lepromatous case.

Diasone therapy:

The patient was placed on diasone on 12.9.46, commencing with 3 tablets a day. His bacteriologic index was 1. By September 1946 there was slight clinical improvement, nasal lesions showed marked improvement by August 1947 and there was further improvement clinically and bacteriologically. The index in August 1947 was 0.5—. Clinical and bacteriological improvement was maintained and by July 1948 the child became negative, index 0, and has remained negative to date (October 1948).

The total amount of diasone taken to the end of October 1948 was 725 grammes.

CASE NO. 17. INDIAN, MALE, AGE 11.

This boy was admitted to the Lady Willingdon Leprosy Sanatorium in July 1944 as a moderate advanced lepromatous case clinically, although bacteriologically the index was only 1. As he showed no marked improvement at the end of two years he was started on diasone.

Diasone therapy:

The patient commenced diasone therapy in August 1946 with 2 tablets a day until September 1947 when he had 3 tablets a day. In October 1946 (after 40 tablets) the patient showed a reaction. This subsided within two months but in March 1947 fresh signs of reaction again appeared, after an additional 242 tablets. By July 1947 the reaction subsided and clinical improvement set in. The tablets were continued during the reactions as is our custom. In January 1948 the index was still 1. During 1948 improvement was slow and the boy is still positive (index 0.5—).

The total amount of diasone taken to the end of October 1948 was 508 grammes.

CASE NO. 18. INDIAN, MALE, AGE 13 (LI).

This child was admitted to the Lady Willingdon Leprosy Sanatorium in December 1945 as an early lepromatous case (index 0.5—). He was placed on routine treatment, maximum weekly

dose 3 c.c.—6 c.c. being given sub-cutaneously and 3 c.c. intradermally. The patient showed no improvement up to August 1946 when he was placed on diasone.

Diasone therapy:

The patient started diasone in August 1946 with 2 capsules a day until August 1947 when he was given 3 capsules a day. On commencement of diasone therapy the bacteriologic index was 1 and the patient complained of nasal blockage. Up to January 1948, while there was clinical improvement, the bacteriological improvement was naturally slight, the index now being 0.5—. During 1948, however, the improvement continued steadily and by September the index was reduced to nil and the patient is therefore negative. The bacteriologic examination was repeated in October 1948 and remained negative.

The total dosage of diasone to the end of October 1948 was 614 grammes.

CASE NO. 19. INDIAN, MALE, AGE 12 (LI).

This child was admitted in October 1944 and placed on routine treatment. The maximum dose was 6 c.c., 4 c.c. being given by the intradermal route. The bacteriologic index at that time was 1. One year eleven months later (September 1946) the bacteriologic index was still 1 but there was considerable clinical improvement and the general impression was that this case would have cleared up with hydnocarpus remedies. He was placed on diasone, however, because he was an early case.

Diasone therapy:

The patient started diasone therapy on 12.9.46. Clinical improvement commenced three months later and by May 1947 the bacteriologic index was 0.5—. By January 1948, however, while there was considerable clinical improvement, he was still positive. Between February and May 1948 clinical improvement continued but the bacteriologic index remained at 0.5—. In June 1948 there was further clinical improvement but the lesions were still slightly positive. In May 1947 the patient was given 3 capsules a day, having been given previously 2 capsules a day.

The patient went on ten days' leave in July 1948 and has not returned.

CASE NO. 20. ANGLO-INDIAN, MALE, AGE 11.

The patient was admitted on 25.5.45 as an early lepromatous case with slight infiltration. His bacteriologic index was 1. He was placed on routine treatment with a maximum dose of 6 c.c. equally divided between the sub-cutaneous and intradermal routes.

After 1 year 4 months there was considerable clinical improvement but less bacteriological improvement (index 1). Considering his racial background and his age it was felt that he was a suitable case for diasone despite the fact that he was slowly, if very slowly, improving.

Diasone therapy:

In September 1946 he was placed on 2 capsules of diasone a day, and in September 1947 he was given 3 capsules a day. In October 1946 there were signs of slight reaction (after 110 capsules). Clinical improvement was noticed by January 1948. During the year there was bacteriological improvement until by September 1948 he had become negative. (Index 0). In October 1948 the bacteriologic index was still negative.

The total amount of diasone taken to the end of October 1948 was 623 grammes.

CASE NO. 21. INDIAN, MALE, AGE 18.

This was a very advanced case of lepromatous leprosy (L3) admitted in March 1941. The bacteriologic index at this time was 4. Between 1941 and 1944 the patient had had very little routine treatment because of persistent and continuous reactions which frequently broke down and left ulcerating surfaces. He was treated along symptomatic lines and given when necessary P.A.T. and mercurochrome. He was almost continuously in hospital for six years. Because he was such an advanced case with little hope of recovery he was put on diasone.

Diasone therapy:

When the patient commenced diasone therapy in August 1946 he had a bacteriologic index of 4. From August 1946 to September 1947 he was given 2 capsules a day and thereafter 3 capsules a day. Clinical improvement commenced in January 1947 and ulcers showed signs of healing. By August they were completely healed and nasal obstruction was relieved. In September 1947 (after he had had 714 tablets) there was a period of three months in which he showed some signs of reaction, although these were mild with occasional pustules breaking out on the lips and face. While the patient's clinical condition improved very remarkably, his bacteriological condition was less rapid in its improvement and in January 1948 the bacteriologic index had only come down to 3. His clinical improvement continues although his index shows no signs of further improvement as yet.

The total amount of diasone taken up to the end of October 1948 was 1040 grammes.

CASE NO. 22. INDIAN, MALE, AGE 11.

This boy was admitted to the Lady Willingdon Leprosy Sanatorium in February 1946 as a moderately early lepromatous macular case. His bacteriologic index on admission was 1.

Diasone therapy:

He was placed on diasone (3 capsules a day) in September 1946 and showed no signs of reaction. By January 1947 the lesions began to subside. He did not really show bacteriological improvement until September 1947 (index 0.5-). Clinical improvement continued but the index remained stationary until the end of August 1948 when the patient became negative with a bacteriologic index of 0. Bacteriologic examination in October 1948 showed that he was still negative. In July 1948 the dose was increased to 4.

The patient had taken a total of 745 grammes at the end of October 1948.

The following further notes were kindly supplied by Dr. Kate Young who was sent a supply of diasone for experimental purposes. It is interesting to note that through a misunderstanding Dr. Young's initial dosages were very high and subsequently reduced to what we would consider too low a level.

CASE NO. 23. INDIAN, MALE, AGE 40 (L3).

The patient was admitted to the Chandag Leprosy Home on 24.2.37. At the time of admission he had had the disease for ten years. On admission he is said to have had nodules on his face and ears. There is no note of throat or nose lesions. He has been on hydnocarpus oil treatment since admission but in inadequate doses. For the last four years he has had throat and nose lesions getting worse in the last six months, and he has been unable to take the oil treatment owing to frequent reactions. In 1945 a metatarsectomy was done because of necrosis of the bone. A persistent ulcer in the foot healed over after this. At the beginning of 1948 his condition was very bad. There was no part of his body unaffected; his feet and hands were swollen; nodules and infiltration were present all over his face and body; there was bossing of his forehead with apparent nodulation of the bone across the whole forehead; his nose was depressed and ulcerated, with practically no septum left; his throat was ulcerated and scarring had closed up the naso-pharynx until there was only a small hole about $\frac{3}{4}$ " in diameter; there was no uvula and ulceration of the larynx with pus oozing from the whole area; breathing was difficult and it appeared that the patient would soon die. On 26th January

1948 his hæmoglobin was 56% (7.8 gms.), his bacteriologic index was 6 and he could only talk with great pain and in a very hoarse whisper and swallow with very great difficulty.

Diasone therapy:

On 26.1.48 the patient was started on diasone, 9 tablets a day with 2 Blands pills. During the first week there was some increase in throat symptoms and complete loss of voice. He was given T. Benzoin inhalations with some relief. On 3.2.48 the patient was very weak and had great difficulty in breathing and swallowing and the dose of diasone was reduced to 6 tablets a day given along with Blands pills and calcium with yeast. By 10.2.48 there was some improvement noticed. Nodules were beginning to break down, his breathing was easier, the œdema of the throat was less and the voice clearer, but he was very weak. One month later the ulcers in the throat had healed, the swelling had practically disappeared and the nodules had flattened. On 27.3.48, when the patient had had 396 tablets, they were stopped for ten days but the calcium with yeast was continued as the patient felt better while taking this. On 6.4.48 diasone was re-started, 1 tablet daily for a week and then 2 tablets daily. On 1.6.48 diasone had to be stopped because of fever, pain in the joints and general weakness. His hæmoglobin at this time was about 8.4 gms. and the total number of tablets taken was 494. On 29.6.48 diasone was re-started, 2 tablets a day until 10.7.48 when this was increased to 3 tablets a day. This dosage was maintained up to 3.8.48 and the total number of tablets taken was 590. On 25.5.48 the bacteriologic index was 4. By this time the patient was comparatively well; nodules had flattened and redness and swelling had disappeared; ulcers had healed; he had no signs of activity in the nose and throat lesions, and no pain; he could speak in a hoarse, but quite loud voice; the nodulation of the forehead was less marked but more obvious to look at because of the decrease in the swelling of the skin in that part. Breathing was normal and he could get about quite comfortably. His clinical condition has steadily improved and, apart from very slight reaction during early October (fever, one or two small nodules on forehead and weakness) which cleared completely within a few days, he has kept well. His bacteriologic index on 19.10.48 was 2.

Up to the end of October 1948 the patient received 284 grammes of diasone.

CASE NO. 24. MALE, AGE 32 (L3).

This patient was admitted to Chandag Leprosy Home on

28.2.36 with a history of leprosy since 1930. On admission he had nodules on face and nose, ears were thickened and there were nodules on forearms, legs and thighs. He had anæsthetic areas on arms, thighs, legs and feet and epistaxis at times. Improvement was slight on hydnocarpus oil injections and in 1944, following a very severe winter, his condition became much worse. Nodules appeared over buttocks, arms, legs and face; he had marked swelling of hands and feet with induration. He has never had lepra reaction. Since 1944 his condition has shown no improvement at all and it has been impossible to give adequate doses of hydnocarpus oil because of fever and weakness. On 28.1.48 he had marked swelling of hands and forearms and of feet and legs. His face was swollen and covered with nodules and his ears were pendulous and nodular. The bridge of his nose was depressed and he had marked crusting and a perforated septum. There were lesions on the hard and soft palate, the uvula was swollen and had lesions on it and on both fauces. His whole body was covered with large, flat, raised macules and infiltration was very marked. His hæmoglobin was 7.8 gms. and his bacteriologic index 6.

Diasone therapy:

On 28.1.48 the patient was started on diasone, 9 tablets a day along with Blands pills. By 10th February some improvement was noted. The swelling of the right hand and of both feet was definitely less. The patient complained of some weakness. Diasone was continued in the same dosage with iron arsenic and strychnine tablets. By 17.2.48 the weakness was less, the patient felt better and his hæmoglobin was the same. On 30.3.48 the swelling of hands and feet was much less and the nodules were breaking down. The patient continued to improve and diasone was continued in the same dosage until 8.4.48 when the patient was given a short rest. On 19.4.48 the diasone was re-started, 1 tablet a day. The patient continued to improve and on 26.4.48 the dose was increased to 2 tablets a day until 2.6.48 when the patient had fever, nausea and ulcerating nodules and the diasone was stopped for one month. By 4.7.48 the patient had recovered from this reaction, his hæmoglobin was 8.4 gms. and he was re-started on diasone, 1 tablet daily. The patient's condition continued to improve, the swelling decreased, nodules flattened and by 17.7.48 there was no ulceration. The dosage was increased on 1.8.48 to 3 tablets a day and the total tablets given up to 3.8.48 was 796. An interesting point in this case was that during the first rest from diasone the most marked improvement set in. There is still some nodulation of the face and ears, but the swelling has gone, lesions of the nose and

throat are healed and the general condition of the patient is very much better. He had considerable iritis previously with loss of vision, which is now very much improved. His bacteriologic index on 29.7.48 was 2. The patient's clinical condition was very much improved by October 1948 and, apart from an abscess on his foot which was opened and healed rapidly, he has kept well. His bacteriologic index on 11.10.48 was 2.

Between 28.1.48 and 30.10.48 the total diasone taken was 307 grammes.

CASE NO. 25. FEMALE, AGE 22 (L3).

This patient was admitted to the Chandag Leprosy Home on 7.2.47. She had a history of four years of the disease, which was first noticed when she had a swelling of the right cheek, hypopigmentation which spread over face and some hoarseness of voice. For about 1 year prior to admission she had enlargement of the cervical glands on both sides and these broke down from time to time, with fever. On admission the patient had nodules on cheeks, nose, ears and on her eyebrows where there was no hair. There was infiltration of the body and swelling of the hands and feet; scars on neck where the glands had broken down; and one small sinus low down on the right side. There was a good deal of hypopigmentation of the face in patches, lesions of the hard and soft palate and on uvula and both fauces. The bridge of the nose was depressed. Treatment with hydnocarpus oil was tried but could not be continued because each time the cervical glands flared up and broke down, with fever and general malaise. Pus was taken to examine for tuberculosis but the bacilli was not found. On 31.1.48 her hæmoglobin was 12.6 gms. and her bacteriologic index was 5.

Diasone therapy:

On 31.1.48 the patient was put on diasone, 6 tablets a day. By 10.2.48 the patient complained of fever and swelling of hands and feet, *but the diasone was continued*. By this time the sinus in the neck had healed over and the general condition of the patient was good. By 20.2.48 the swelling of the feet was more marked and there were nodules along the outer edges. By 23.3.48 the swelling had practically gone and the glands were completely healed. By 24.5.48 the patient had continued to improve slowly and steadily and was then given a rest for two weeks. On 9.6.48 diasone was re-started, 2 tablets a day, the dose being increased to 3 tablets a day on 1.7.48, when the feet started to swell again. On 21.7.48 the dose was increased to 4 tablets daily, when there

was some improvement and the swelling less. On 29.7.48 fresh nodules appeared on arms and thighs but the patient's general condition was good. By 3.8.48 there was some improvement and the swelling was less. The total number of tablets taken to 3.8.48 was 851 and the bacteriologic index on 17.7.48 was 3. Her clinical condition has steadily improved all the time. Sinuses in the neck, which had been persistently recurring, have not shown any signs of activity; nodules on the face have completely disappeared leaving hypopigmented patches; there are still nodules on the feet and some infiltration of the body but this is much less. On 19.10.48 the bacteriologic index was 1.

The total diasone given to the end of October 1948 was 381 grammes.

CASE NO. 26. FEMALE, AGE 31 (L3).

This patient was admitted to the Chandag Leprosy Home on 25.12.46 with a history of nodules on face, ears and hands, and some neuritis for one year. Four months prior to admission she had had a long deep ulcer of the right leg affecting the bone, about 6" long and $2\frac{1}{2}$ " wide. This was scraped and necrosed bone removed and it gradually healed on sulphanilamide treatment locally and hydnocarpus oil injections. On admission there were small, discrete, nodules over face, arms, legs and buttocks. There was no depression of the nose, but marked crusting and frequent epistaxis. There were lesions on the hard and soft palate, on the fauces and uvula and also some nodulation of the vocal cords. The left leg was swollen and painful. There was no improvement of the lepromatous condition with hydnocarpus treatment and the patient had frequent reactions which interrupted treatment and which left residual fresh nodules. During these reactions the chief symptoms were swelling of the face, with fever, acute conjunctivitis and iritis. On 3.2.48 the patient's hæmoglobin was 11.2 gms. and the bacteriologic index was 5.

Diasone therapy:

The patient started on diasone, 6 tablets a day, on 2.2.48. By 10.2.48 she had developed slight fever and swelling of the face, and on 17.2.48 she had conjunctivitis with profuse lachrymation and slight cyanosis. *The diasone was continued during this time*, but stopped on 22.2.48 when the patient had a high fever with rigor for which she was given quinine. By 25.2.48 the fever had subsided, the eye appeared normal and the patient was re-started on diasone, 6 tablets a day. This treatment continued until 10.3.48 when the eye symptoms recurred with fever and the patient was

put on rest for eight days. Diasone was re-started on 18.3.48 with a dose of 3 tablets a day. There was no further reaction and some slight clinical improvement during the next two months. On 18.5.48 the diasone was stopped for rest of three weeks and the patient was re-started on 9.6.48 on a dosage of 2 tablets a day. Up to 3.8.48 she had a total of 525 tablets. From January to August 1948 there was slow improvement. The nodules were less and those that remained in August were flattened and less definite in outline. The patient by August had no eye trouble, lesions on throat and palate had practically disappeared and her general health was good. Her hæmoglobin has remained about the same throughout treatment. The bacteriologic index on 29.7.48 was 2. Clinical improvement was slow but steady. There are now no eye symptoms at all and nodules are flattening. On 18.10.48 the bacteriologic index was 1.

The total diasone received up to the end of October 1948 was 242 grammes.

CASE NO. 27. MALE, AGE 36, from Nepal (L3).

This patient was admitted to the Chandag Leprosy Home on 18.2.47 with a history of ten years' leprosy. Patient had first had sores on his feet, frequent bouts of fever with swelling of the face and limbs and blisters on his legs and thighs. Five years previously his face became nodular and he had crusting of the nose with deformity. On admission he had a typical lionine facies with nodules along the eyebrows and on the cheeks; infiltration of the skin over the whole of the body, with reddening of the skin and pendulous nodular ears. There was a small perforation of the septum of the nose and crusting was very marked. He had lesions on the hard and soft palate and slight nodulation of the fauces, vocal cords and epiglottis. but no ulceration of the throat. He was put on hydnocarpus oil treatment but showed no improvement at all. On 24.2.48 his hæmoglobin was 13.2 gms. and his bacteriologic index was 4.

Diasone therapy:

On 24.2.48 the patient was given diasone, 9 tablets a day, but on 5.3.48 the dose was reduced to 6 tablets a day because of reaction. On 19.3.48 the diasone was stopped as the nodules on face had become septic, the periphery of which was inflamed, and the patient had become very weak with fever and cyanosis. The patient was given coramine injection and put on to calcium with yeast. By 13.4.48 the patient was very much better, the nodules had flattened out and the general condition was good. Diasone

was re-started, 1 tablet daily. Flattening continued, general health was good and the dose on 1.5.48 was increased to 2 tablets daily. During the next three months the patient continued to improve slowly and by 20.7.48 the infiltration was less and there was no redness. The dose was increased to 3 tablets daily. The patient had taken a total of 405 tablets on 3.8.48. His hæmoglobin fell to 11.2 gms. in the first month and then remained at approximately 13.4 gms. throughout. The bacteriologic index on 20.7.48 was 1. Clinical improvement was steady. Diasone had to be stopped during September because of urinary symptoms. There are no such symptoms now and the patient is taking 4 tablets daily. On 19.10.48 the bacteriologic index was 1.

Up to the end of October 1948 the patient received 210 grammes of diasone.

CASE NO. 28. FEMALE, AGE 17.

This patient was admitted to the Chandag Leprosy Home on 26.1.48 with a history of swelling of skin of face over the cheek bones and erythema, also swelling of feet and hands, for a period of six months. She had had no fever. On admission there was swelling of the face, hands and feet, no nodulation, no lesions of the nose or throat. She had no deformity although occasionally she had slight pain in the ulnar nerves. The patient did not improve on hydnocarpus injections. On 15.3.48 her hæmoglobin was 13.4 gms. and her bacteriologic index was 4.

Diasone therapy:

The patient was put on diasone on 15.3.48, two tablets daily. By 1.4.48 the swelling was less, the general health good and the dose was increased to 3 tablets daily. There was a break in treatment from 19.6.48 to 28.6.48 when the patient had worms and diasone was stopped to treat these. The patient started diasone again on 28.6.48 on a daily dose of 1 tablet which was increased on 7.7.48 to 2 tablets a day. By this time the swelling had practically gone. On 12.7.48 there was inflammation of the left ulnar nerve above the elbow, with pain, thickening and fever. Sodium salicylate was given with local application of ichthyol. On 21.7.48 the patient was much better and the dose of diasone was increased to 3 tablets a day. On 26.7.48 the patient again developed severe pain and tenderness of the left ulnar with marked thickening and fever. Sodium salicylate was given again, but there was no improvement so diasone was stopped on 27.7.48 and antiphlogistine applied. Sodium salicylate was continued. By 2.8.48 the patient

was much better. The nerve was much less swollen and the pain gone, but there was some swelling of the feet with small nodules appearing on the shins. Diasone was re-started, 1 tablet daily. The total diasone taken up to 3.8.48 was 334 tablets. The bacteriologic index on 27.7.48 was 2. There was marked clinical improvement but severe reaction with pain and swelling of the ulnar nerve led to diasone being stopped for 6 weeks during August and September. When it was started again on 8.9.48 the patient showed more satisfactory tolerance and the clinical condition, which had worsened again, began to improve. The bacteriologic index on 26.10.48 was 1.

The patient has taken 151 grammes of diasone up to the end of October 1948.

NOTE.

It is interesting to note that about 30% of all cases under diasone treatment showed reaction signs, some of them severe, but by the time 700 tablets were administered these reaction signs were reduced considerably and no case went into reaction after the administration of 1,000 tablets. This confirms our view that the sulphone remedies should be continued in spite of reaction, and that probably there is a reaction phase through which patients have to go before the remedy begins to have a bacteriostatic effect on the bacilli. This reaction phase may be so slight as to pass unnoticed or it may be so severe as to necessitate the temporary discontinuance of treatment. The reasons for this reaction will be discussed at the conclusion of this paper.

It is further interesting to note that the total number of tablets of diasone which were given over this period were very considerable and that the only cases which have become negative were among the boys. No adult case as yet is negative. This suggests that the higher the dosage of diasone the better, for it is assumed that as the boys have been taking doses within the adult limit the amount of grammes per kilo of body weight has been considerably more than that given to adults; hence the more rapid improvement. It is therefore suggested that diasone should be pushed to the limit of tolerance, but unfortunately the remedy is so expensive that few could afford to be given more than 4 tablets a day.

CASES GIVEN SULPHETRONE.

In September 1946 sulphetrone was received for clinical trial and the following is a summary of the report of cases given this drug.

CASE NO. 29. INDIAN, MALE, AGE 28.

This was a case of moderately advanced lepromatous leprosy (L2) with macular lepromatous leprosy and infiltrated lesions on elbows, upper arms, thighs and buttocks and with nasal blockage. He had been under hydnocarpus treatment for three months and had reached a maximum dose of 9 c.c. His bacteriologic index was 2.

Sulphetrone therapy:

Sulphetrone was commenced on 16.10.46. In the initial stages the increase of dosage was slow, a total of 6 grammes a day being reached at the end of the third week. Apart from a mild reaction (after approximately 60 tablets had been given) five weeks later, the drug was well tolerated. Iron and yeast were given along with the tablets. Clinical improvement commenced twelve months after sulphetrone administration was started. The skin had lost its shiny appearance as seen in lepromatous leprosy and the bacteriological improvement commenced one year after the administration of sulphetrone, although after three months bacilli began to show fragmented forms. In November 1947 the bacteriologic index was 1. By January 1948 the index was still 1. The patient continued on sulphetrone and was transferred to the Lady Willingdon Leprosy Sanatorium in April 1948. Clinical improvement continued more rapidly than bacteriological improvement and it is now difficult to recognise any lesions. His bacteriologic index in October 1948 was 0.5 - .

The total amount of sulphetrone given up to the end of October 1948 was 3,775 grammes.

CASE NO. 30. INDIAN, MALE, AGE 31.

A very advanced lepromatous case with marked nodulation and infiltration. Nodules were particularly noted on face, ears, and buttocks. The patient presented himself for treatment at the Leprosy Department, General Hospital, Madras, in November 1946 and as far as is known received no previous treatment with hydnocarpus preparations.

Sulphetrone therapy:

On 11.11.46 sulphetrone was commenced and the maximum dosage was reached within 3 weeks. While the patient showed periodically slight signs of reaction, he complained of marked nerve pain from time to time. The nerve pain was difficult to control and had to be relieved on at least one occasion by an alcohol injection. In February 1947, owing to nerve pain the drug was

discontinued for three weeks. Apart from that the drug has been continuously administered. Along with the sulphetrone, the patient was given iron and yeast in adequate dosages. His blood picture has remained satisfactory. After 8 weeks the patient began to show some clinical improvement with healing of the open ulcers, flattening out and subsidence of nodules and his nasal lesions and symptoms of blockage were considerably relieved within three months. Clinical improvement continued and was very marked. Bacteriological improvement, however, was very much slower. The bacteriologic index in November 1946 was 4; one year later it was 3; in June 1948 it was still 3. The bacteriologic index did not begin to show definite decrease until July 1948 and by October 1948 it had only been reduced to 2. The interesting feature of this case is that the clinical improvement is now so great that it would be difficult to recognise him as a case of leprosy (vide photographs), but his bacteriologic index is not below 2, although all smears show markedly fragmented bacilli and have been fragmented for over six months. The patient had no definite febrile periods. His reactions showed themselves in persistent and severe nerve pain which continued for eighteen months. While the nerve pain has largely subsided it cannot be said that he has been completely relieved of this distressing symptom.

The total amount of sulphetrone taken to the end of October 1948 was 3,203 grammes.

CASE NO. 31. INDIAN, MALE, AGE 19.

A case of moderately advanced lepromatous leprosy. He had previously had ten months' treatment with hydnocarpus oil, with a maximum dose of 11 c.c.—5 c.c. hydnocarpus oil sub-cutaneously and 6 c.c. ethyl esters intradermally.

Sulphetrone therapy:

Sulphetrone was commenced in October 1946. After the first three weeks the patient showed mild reaction (30 tablets). The blood level at the time appeared to be higher than usual and therefore the dose was reduced for some time to 8 tablets a week. Eight weeks after the commencement of sulphetrone therapy the patient began to show some improvement as evidenced by fading of the macules and slight subsidence of infiltration. The patient continued to improve clinically. The bacteriologic index had not shown improvement commensurate with the clinical condition but the bacilli were fragmented. On admission the index was 1; at the end of seven months it was 2. By January 1948, however, seven months later, the clinical improvement continued and the patient

ILLUSTRATIONS.

CASE No. 30. (p. 27) Case under sulphone treatment.

FIG. 1. Condition of patient before treatment on 11.11.46.

FIG. 2. Same six months later. Bacteriologic index has not improved.

FIG. 3. Same case October, 1948, with markedly fragmented bacilli. (p. 28).

CASE No. 7. (p. 10) Treated with diasone.

FIG. 4. Case on commencement with treatment, Aug. 1946.

FIG. 5. Same case after two years' treatment.

CASE No. 43 (p. 38) Treated with injected sulphone.

FIG. 6. Case on commencement of treatment, Nov. 1947.

FIG. 7. Same case four months later.

FIG. 8. Same case after 11 months' treatment.

CASE No. 51 (p. 44) Treated with sulphetrone emulsion.

FIG. 9. Case on commencement of treatment, 11.1.48.

FIG. 10. Same case 9 months later.

CASE TREATED WITH SULPHONE EMULSION.

FIG. 11. Case on commencement of treatment.

FIG. 12. Same case six months later.

CASE TREATED WITH 50% AQUEOUS SULPHETRONE.

FIG. 13. Case on commencement of treatment.

FIG. 14. Same case after 8 months' treatment.

FIG. 15. Same case after one year's treatment.



FIG. 1.



FIG. 2.



FIG. 3.

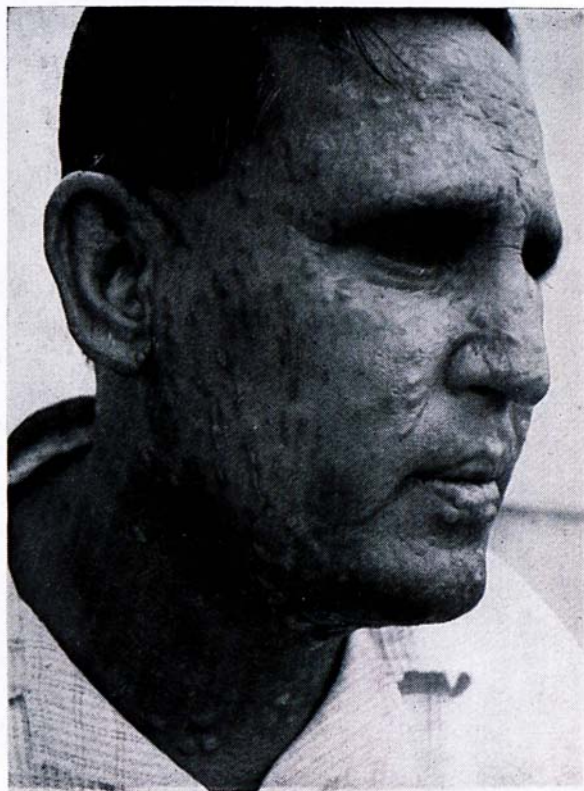


FIG. 4.



FIG. 5.



FIG. 6.

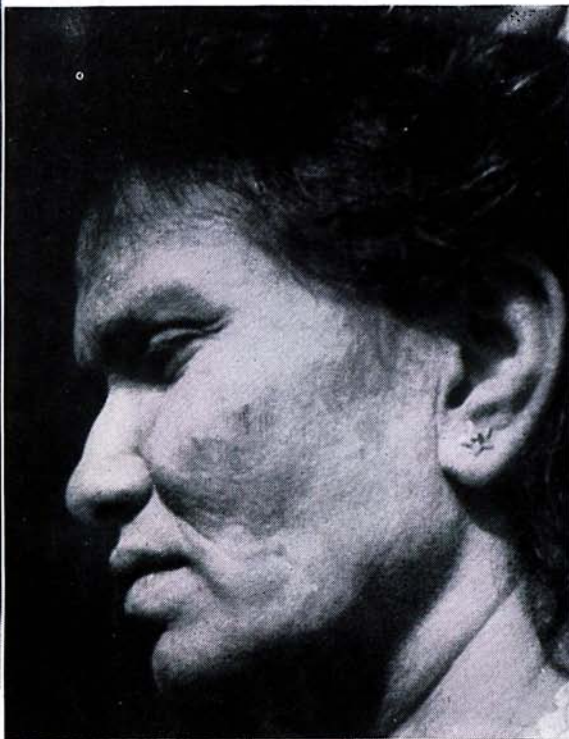


FIG. 7.



FIG. 8.

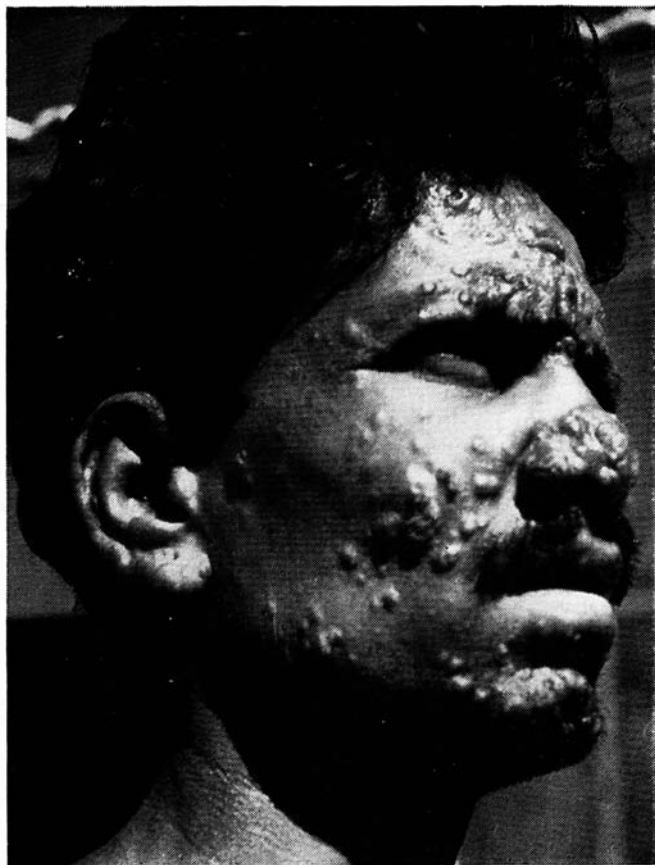


FIG. 9.

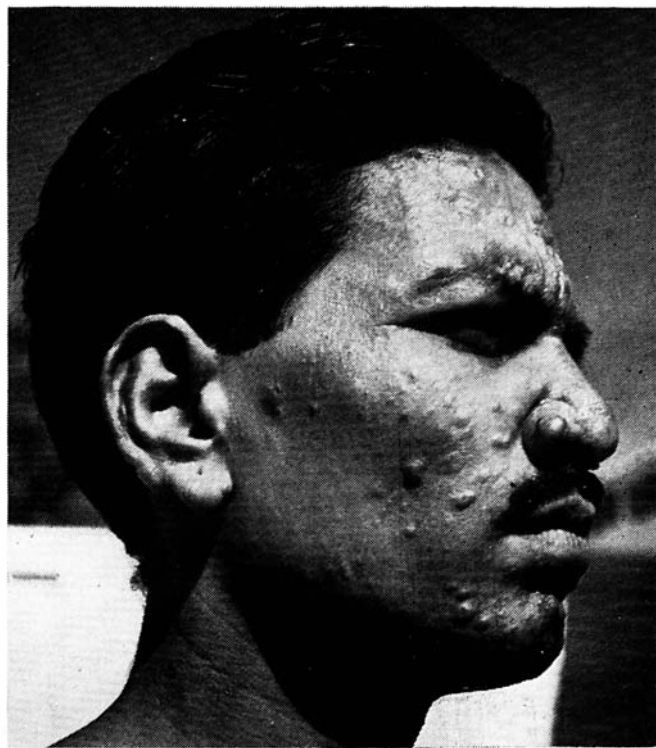


FIG. 10.

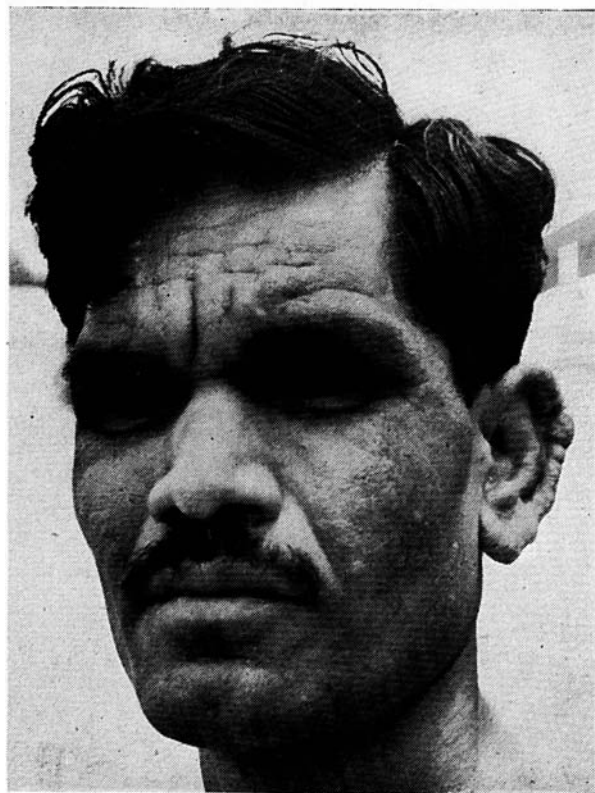


FIG. 11.

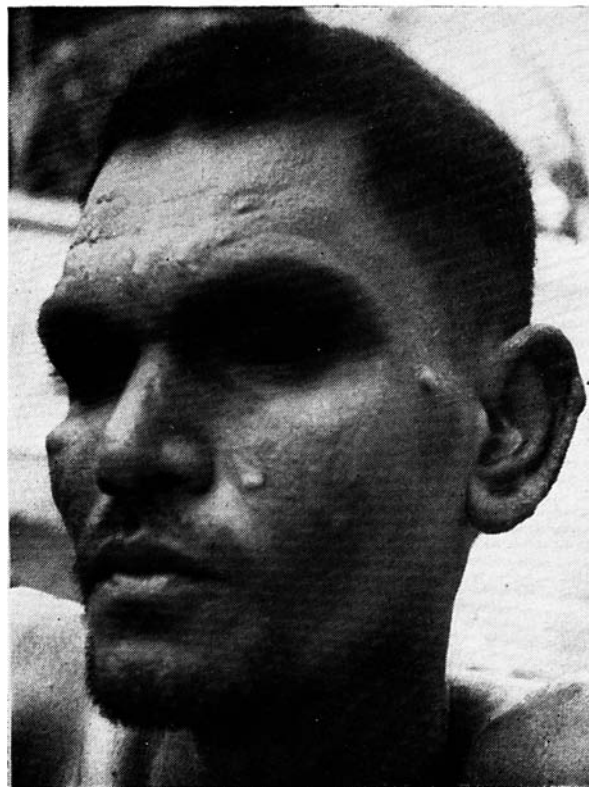


FIG. 12.



FIG. 13.

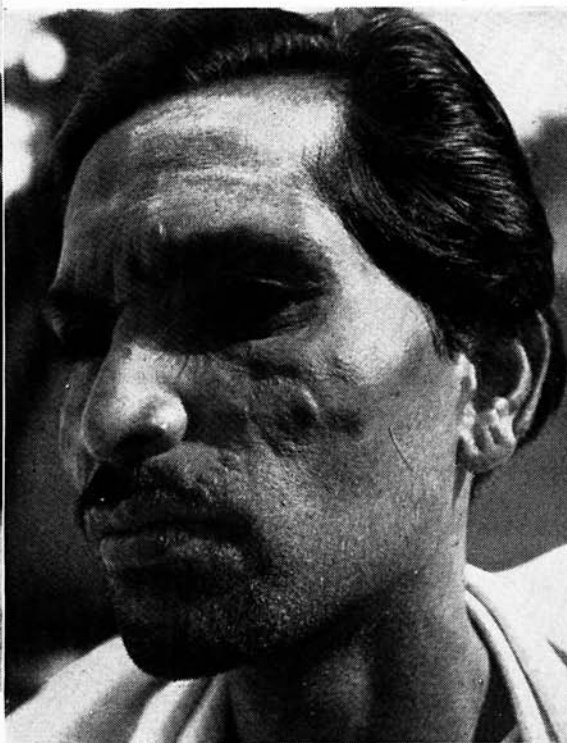


FIG. 14.

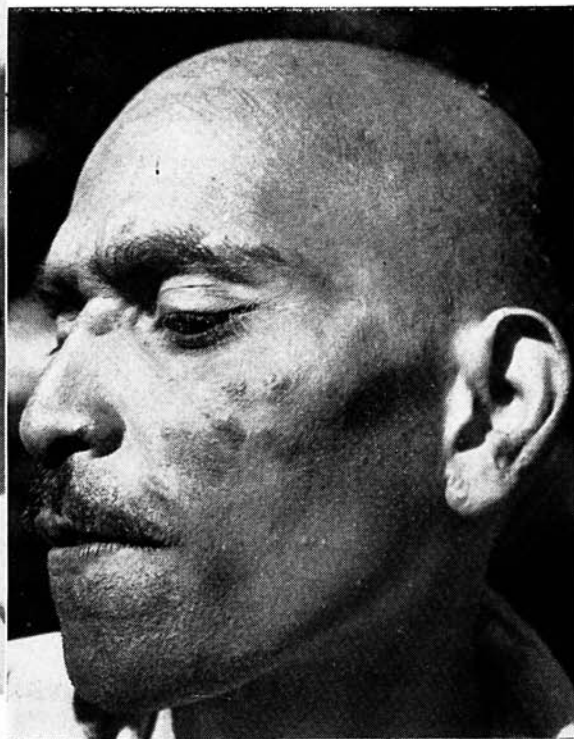


FIG. 15.

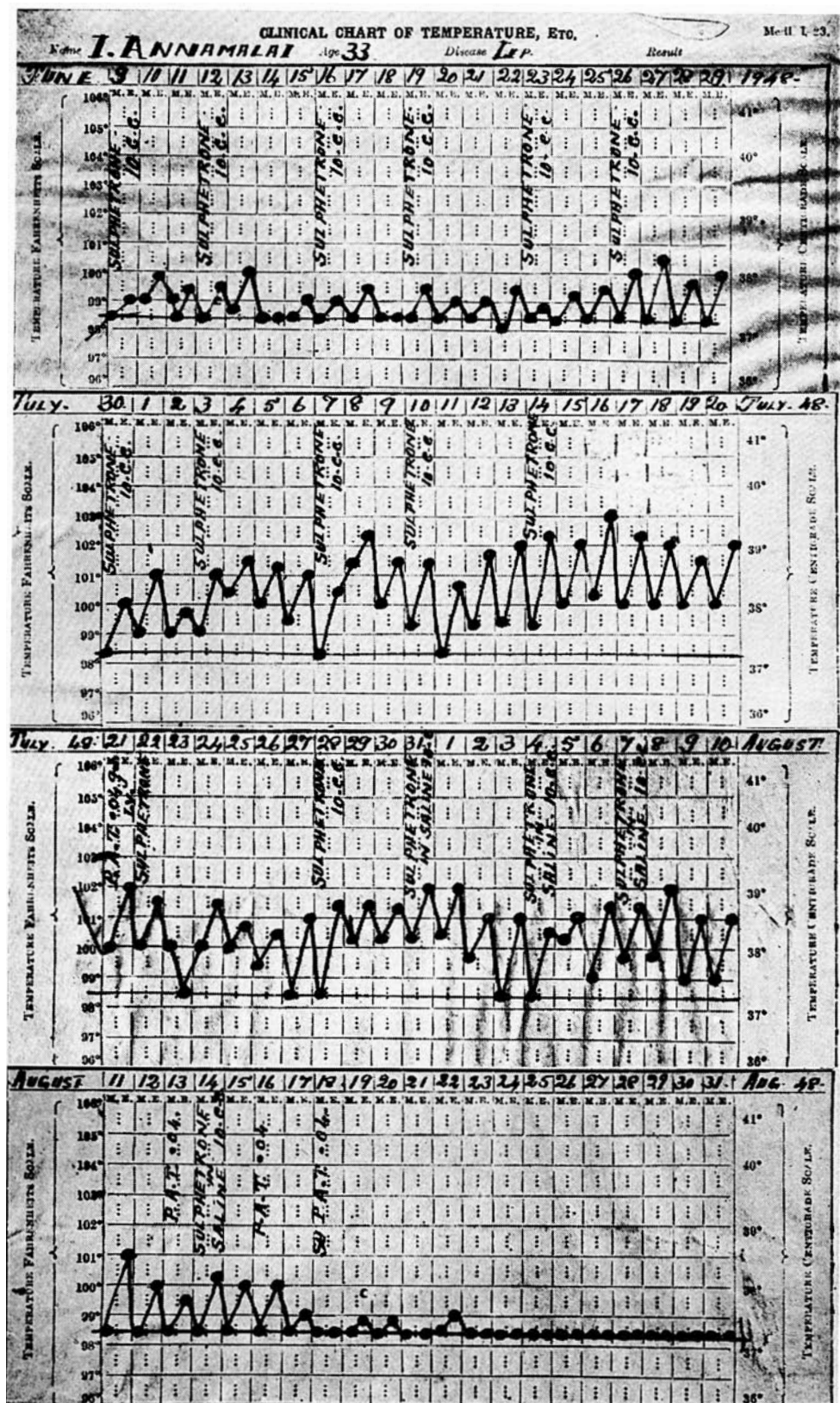


Illustration of temperature chart showing cessation of fever on continued administration

showed marked bacteriological improvement, the index being 0.5 -. In October 1948 the patient had become negative.

The total amount of sulphetrone taken to the end of October 1948 was 2,500 grammes.

CASE NO. 32. INDIAN, MALE, AGE 20.

This was a moderately advanced lepromatous case of seven years' duration with thickening of cheeks and chin infiltrated. There were erythematous lesions of the trunk and extremities which were also slightly infiltrated. The ulnars and peroneals were thickened. The patient had regular treatment with hydnocarpus remedies for seven years, reaching a maximum dosage of 5 c.c. hydnocarpus oil sub-cutaneously and 5 c.c. ethyl esters intradermally, but showed no improvement.

Sulphetrone therapy:

The patient was placed on sulphetrone on 28.1.47 with a commencing dose of 3 tablets a day, gradually increasing to 12 tablets a day, and this was maintained continuously. After about four months the patient began to show clinical improvement although bacteriological improvement was much less marked. The bacteriologic index on commencement of sulphone therapy was 3; after four months it was 1 and by August 1948 it had become negative and has remained negative. This patient developed cyanosis four months after the commencement of sulphetrone. The significance of cyanosis at the time was not understood and the tablets were withheld for one week. The cyanosis disappeared and has not recurred. In July 1947 there was severe albuminuria, when sulphetrone treatment had to be suspended. The patient was treated along routine lines and the condition cleared up one month later and sulphetrone tablets were re-started, 6 tablets per day. During May 1947, after 380 tablets had been taken, the patient showed a mild reaction with swelling of the ear lobes. This cleared up in the course of a few days. The patient made steady progress.

The total amount of sulphetrone taken up to the end of October 1948 was 2,110 grammes.

CASE NO. 33. (Private patient) EUROPEAN, MALE, AGE 60.

This case was first seen in October 1945 when he was a moderately advanced macular lepromatous case, showing extensive macular lesions and infiltrated lesions in the neck associated with anæsthesia in the area of the ulnar and peroneal nerves. He was placed on intensive intra-dermal and sub-cutaneous treatment,

being given a total of 15 c.c. a week—5 c.c. hydnocarpus oil sub-cutaneously and 10 c.c. ethyl esters intradermally. By December 1946 he had improved a very great deal and only one smear showed a few broken bacilli. In January 1947, however, the smears showed slight deterioration and by March his clinical condition had definitely deteriorated. Because of the race and the severity of the prognosis the patient was placed on sulphetrone in March 1947.

Sulphetrone therapy:

This was commenced in March 1947 and the patient took approximately three weeks to reach the maximum dose. During the first week marked cyanosis was seen and the patient became a dark plum colour, but he was advised that sulphetrone should be continued. The cyanotic appearance gradually faded and had completely disappeared by August 1947. The patient increased tablets each week until 12 tablets per day were given and continued without a break and without any symptoms until December 1st 1947 when the drug was discontinued because the R.B.C's fell to 3.3 million and the hæmoglobin to 10 gms. Large doses of yeast (12 tablets Squibbs yeast daily) were given. On commencement of sulphetrone the bacteriologic index was 1. By November 1947 the bacilli showed considerable fragmentation, some smears showing only acid fast dust, and the bacteriologic index was 0.5—. In December 1947 the patient was given a month's rest at the end of which time he was started again with 4 tablets a day, increasing by 2 tablets every 2 days until the 12 tablets per day was reached. For one week there was slight cyanosis but no toxic signs. During the whole of the administration of sulphetrone, yeast tablets (12 a day) were given, but except during the period when he showed a fall in his red cell count and hæmoglobin, iron was not administered. In July 1948 the patient showed his first negative.

The total amount of sulphetrone given was 3,300 grammes.

CASE NO. 34. (Private patient) INDIAN, MALE, AGE 27.

This patient was first seen in 1937 and placed under intensive hydnocarpus treatment—maximum dosage reached 15 c.c. per week, 5 c.c. sub-cutaneously and 10 c.c. esters intradermally. The patient improved and became negative in 1940, but in 1941 he relapsed and from 1941 to 1946 showed very little improvement. In 1946 he began to deteriorate clinically and bacteriologically somewhat rapidly.

Sulphetrone therapy:

He was placed on sulphetrone in August 1946. In October

1947 he had a severe reaction (after more than 3,000 tablets) and had nerve pain which confined him to bed. The pain was particularly confined to the peroneal and ulnar nerves. During this period of reaction his white cell count increased to 15,000 with a polymorphonuclear increase up to 88%. The ulnar nerve pain in particular was relieved by a few exposures of deep x-ray therapy. The patient's bacteriologic index on commencement of treatment was 1. While clinical improvement was marked, bacteriological improvement was slow and by January 1948 the index was still 1. In June 1948 the patient had another attack of nerve pain, this time very severe, and curiously enough within 48 hours, as the result one assumes of œdema and pressure on the peroneal nerve, he developed drop foot. Owing to the seriousness of the prognosis of this condition in leprosy and the danger of further damage due to reaction, sulphetrone was discontinued and he was put under specialist orthopædic treatment. By October 1948 his drop foot began to improve and the muscles have largely recovered their function. His clinical condition has not deteriorated and his bacteriologic index has remained the same. It has been decided to suspend further sulphetrone medication until the maximum recovery of his foot has been obtained.

The total amount of sulphetrone taken was approximately 3,000 grammes.

(This case is included in these records as an example of drop foot occurring suddenly in leprosy as the result of lepra reaction. It is of interest to note that while drop foot occurring during the course of the disease does not recover, recovery in this case has begun, showing that probably the pathological condition was due to pressure as the result of œdema in the sheath and not to complete destruction of the nerve fibres.)

CASE NO. 35. (Private patient) INDIAN, MALE, AGE 44.

This was a very advanced case of lepromatous leprosy with numerous nodules, advanced nasal lesions, ulceration and signs of iridocyclitis. The patient had had leprosy since he was a boy of 14. The senior author was first consulted in 1942, when the patient was placed on hydnocarpus treatment and in addition carbon dioxide snow was applied to the more obvious nodules and his ears were made more shapely by a minor surgical operation. From 1942 to 1944 the patient showed slow improvement but very little difference in his smears. Unfortunately, owing to the occupation of the patient and his status in society, it was difficult to secure a sufficient number of smears on which to work out a bacteriologic

index. This therefore cannot be given. All the smears, however, that were examined were 5+ and 6+ positive.

Sulphetrone therapy:

In August 1946 sulphetrone was commenced, the maximum dose being reached within two weeks. Apart from a slight reaction about six months later (after approximately 2,000 tablets) which showed itself in an attack of iritis, the patient has had very little trouble. He has taken in addition yeast and iron in the form of Fersolate. The patient's clinical condition continued to improve and the bacilli showed fragmentation. In August 1948 the patient showed his first negative. This case showed very remarkable improvement considering his advanced lepromatous condition and, as was expected, his nasal lesions, which were severe, responded more rapidly than his skin lesions.

The total amount of sulphetrone taken to the end of October is approximately 3,750 grammes.

CASE NO. 36. (Private patient) INDIAN FEMALE, AGE 33.

This was a moderately advanced lepromatous case showing diffuse macular lesions and many sub-cutaneous nodules, with a marked tendency to reaction, during which time numerous rose-spot nodules were noted. The patient was first seen in October 1945 and placed on routine hydnocarpus treatment. She was only able to take small dosages owing to reaction. From October 1945 to August 1946 her clinical condition had not improved and the reaction phase was maintained.

Sulphetrone therapy:

In August 1946 she was placed on sulphetrone, reaching the maximum dose of 10 tablets in two weeks. During the first six months of treatment the patient showed continuous reaction of a mild nature, the evening temperature rising to 101°. Sulphetrone was continued in spite of this and gradually the patient passed out of the reaction phase. It was impossible to take a sufficient number of smears to calculate the bacteriologic index, but within three months the bacilli became fragmented and the patient was first negative in July 1948 and has remained negative since.

The patient had approximately 3,500 grammes of sulphetrone to the end of October 1948.

CASE NO. 37. ANGLO-INDIAN, MALE, AGE 30.

This patient was first admitted into the Lady Willingdon Leprosy Sanatorium in November 1936 as a moderately advanced

lepromatous case. He was under treatment for five years and showed considerable clinical improvement under hydnocarpus therapy (maximum weekly dose 15 c.c.—10 c.c. hydnocarpus oil sub-cutaneously and 5 c.c. ethyl esters intradermally). He left the Sanatorium on his own account in December 1941 when only two smears were slightly positive. In July 1942 he returned to the Sanatorium and was admitted as an early lepromatous case with a few macular lepromatous lesions. The bacteriologic index on admission (July 1942) was 1. He was placed on routine hydnocarpus treatment but this time only reached a maximum dose of 12 c.c. divided equally between the sub-cutaneous and intra-dermal routes. In spite of treatment the patient gradually deteriorated both clinically and bacteriologically and five years later his bacteriologic index was 2.

Sulphetrone therapy:

In May 1947 he was placed on sulphetrone, taking three weeks to reach the maximum dose of 12 tablets a day. In August 1947 (after 1,300 tablets) he developed rather severe lepra reaction accompanied by a severe attack of iritis. His treatment, however, continued. At the end of September the iritis had recovered and the lesions had begun to show definite clinical improvement. Bacteriological improvement did not set in until January 1948, when the index was 1. In October 1948 the bacteriologic index was 0.5—. The patient showed steady clinical improvement and except for the reaction described showed no toxic signs. He was given yeast in addition to sulphetrone, but no iron.

The total amount of sulphetrone taken to the end of October 1948 was 3,000 grammes.

NOTE.

It will be noted that with oral sulphetrone only one case had a very severe reaction. In this one case the reaction affected a nerve mainly and caused drop foot. It is therefore necessary to issue a note of caution that should severe nerve pain occur in the peroneal nerve, treatment should be stopped at once to prevent trauma to the nerve fibres and consequent paralysis. Apparently the paralysis is different from that produced in the course of leprosy in that it is recoverable after about five or six months. It must be admitted that the patient in question received vigorous treatment in the form of electro-therapy, massage and splinting and was supplied with a special boot.

The most interesting comment is that out of nine cases, four became negative within a period of two years:

INJECTABLE SULPHONES.

Owing to the inconvenience of administering large doses of the sulphones (diasone, sulphetrone) orally because of the impracticability of this method of treatment except in institutions where the patients are strictly regimented, and owing to the cost of the treatment making it quite impossible to use it in mass treatment, experiments were commenced on the possibility of injecting certain preparations of the sulphone derivatives. It is, of course, realised that the first injectable-sulphone which was used was promin (1943), but it is manifestly inconvenient to use a preparation which necessitates intravenous injections every day of the week, and further, in our limited experiments with promin, apart from the impracticability of organising large scale intra-venous injections in Indian institutions, we found that Indians showed a tendency to toxic signs with promin—namely, anæmia, general weakness, etc.—and that the response to treatment was not any more rapid than that given by mouth. Because of the fact that the active principle in all these derivatives is almost certainly the parent substance, diamino-diphenyl-sulphone, it was decided to use a suspension of this drug in oil. The oil that was chosen was ground nut oil owing to its cheapness and ready availability. Preliminary experiments were first started on a 15% suspension given intradermally, because it is held by the senior author that if the bacilli can be prevented from multiplying in the skin the disease will not progress. When it was found that the substance not only was discovered in the skin of the area which was given intradermal injections but also elsewhere in addition, it was felt that it probably was not worth the pain of the injection, for the same effect could be produced by sub-cutaneous injections.

The original work on skin concentration of the drug was vitiated by the fact that it was discovered later that the local anæsthetic which was used, namely novocain, gave a colour reaction when tested with the reagents and placed in the photo-electric colorimeter. The work on skin excretion and concentration of the drug will therefore have to be repeated. Nevertheless, as will be stated later, the drug is found in appreciable quantities in the skin.

The following cases are illustrative of those who have received a suspension of diamino-diphenyl-sulphone for more than six months.

CASE NO. 38. INDIAN, MALE, AGE 25.

This patient was a moderate lepromatous case with infiltrations

of ear, forehead and lepromatous macular lesions throughout the body. He had no treatment prior to sulphone therapy.

Sulphone therapy:

The patient commenced sulphone therapy in March 1947. He was first placed on a 15% diamino-diphenyl-sulphone suspension by intradermal injection. This was later substituted by a 50% suspension but, as this was found to be too thick, the suspension was reduced to 25%. He was placed on intradermal injections for approximately two months. When it was found that the sulphone was probably deposited in the skin in the area which was not intradermally, it was felt that the sub-cutaneous route would be less painful and more easy of administration. The dose which was ultimately chosen was 5 c.c. of a 25% suspension of diamino-diphenyl-sulphone twice a week, giving a total of 2.5 grammes in the week. The patient continued on sulphone therapy almost continuously until 11.10.48 when he was given one month's rest. The blood level was between 0.7 and 1.8 mgm%. No complications were evidenced during the whole course of the treatment. Clinical improvement commenced approximately three months after the start of the treatment and continued progressively. The bacteriologic index, which was 2 at the commencement of the treatment, began to show improvement three months later when it was 1 and became negative twenty months later. As in some cases, there was no deterioration of the smears at any time.

The total dosage to the end of October 1948 was 111 grammes.

CASE NO. 39. INDIAN, MALE, AGE 40.

This patient was a moderately advanced lepromatous case who had had leprosy for at least 15 years and showed macular lepromatous lesions associated with areas of infiltration and thickened ear lobes. The maximum dose of hydnocarpus oil and ethyl esters reached was 5 c.c. During the years in which he received hydnocarpus treatment he showed little deterioration but no improvement and therefore was chosen for sulphone therapy.

Sulphone therapy:

The patient was placed first on a 50% suspension on 14.10.47, 1 c.c. sub-cutaneously, and this was gradually increased to 5 c.c. per week. From February to April 1948 treatment was suspended owing to the development of severe reaction and severe anæmia—after taking approximately 20 grammes of the drug. When the anæmia set in his blood level was over 2 mgm%. He was given intensive iron and yeast therapy with a good response. His treatment was resumed in May and continued until the middle of July

when again it had to be stopped due to severe anæmia (red cells 2.8 and hæmoglobin 8 gms). Up to this time the total amount of drug taken was 31.5 grammes. His treatment was resumed three months later (October 1948) and it is interesting to note that three months after the cessation of treatment traces of the drug could still be detected in the blood. On commencement of treatment the bacteriologic index was 3. Three months later it had shown improvement and was 2, but after two months the bacteriologic condition deteriorated further and was again 3. This is not an uncommon finding in the initial stages of sulphone therapy. From February 1948, despite the anæmia which has been described and which necessitated the stoppage of treatment, the clinical and bacteriological condition still improved and by the end of September 1948 the index fell to 1.

The total amount of drug given to date is 40 grammes.

CASE NO. 40. INDIAN, MALE, AGE 26.

This patient has had a history of leprosy of five years' duration and has had regular treatment with hydnocarpus remedies during this period. The patient was a diffuse lepromatous case with a bacteriologic index at the commencement of treatment of 3. (October 1947.)

Sulphone therapy:

Sulphone therapy was commenced with a dose of 1 c.c. of 50% suspension which was increased to 5 c.c. once a week. From February 1948 to April 1948 he was placed on rest owing to anæmia (2.5 millions) and neuritis. He was re-commenced on 5.4.48 with a dose of 3 c.c. and continued until 20.9.48 when he was given further rest. (Blood 2.5 millions; hæmoglobin 10 grammes.) The clinical improvement, despite reactions and neuritis, was steady and his bacteriologic index on 11.10.48 was negative. This case was rather remarkable in the fact that he received so much rest. The neuritis which developed was very severe but responded to a preparation known as Astmopil.

The dosage in grammes given in the 12½ months' treatment was 68.

CASE NO. 41. INDIAN, MALE, AGE 26.

This patient had a history of ten years' duration. He has had regular but interrupted treatment with hydnocarpus oil for four years but had no treatment for the six months prior to the commencement of sulphone therapy. The patient was a moderately early lepromatous case with a few slightly infiltrated, poorly

defined macules over the cheeks, lower back, buttocks and knees. The left ulnar and both peroneals were thickened and tender.

Sulphone therapy:

Sulphone therapy was commenced on 20.10.47 (50% suspension) with a dose of 1 c.c. which was gradually worked up to 5 c.c. per week. He continued until the end of February 1948 when he was given two months' rest. The patient re-commenced treatment in April 1948, but at the beginning of May (after taking 35 grammes approximately) treatment had to be withheld due to development of weakness, vomiting and nausea. After resting for one month he was put back on sulphone therapy in June, but again after four weeks the same symptoms recurred. The patient was advised to rest and has not returned for further treatment. Up to the time at which the patient left the clinic, his clinical and bacteriological condition improved steadily. On commencement the bacteriologic index was 4 and ten months later it was 1. The blood level at one stage reached 2 mgm%. At no time did the patient show anæmia, but he showed other toxic signs in the form of severe headache, giddiness, vomiting and weakness.

The total quantity of drug given was 40 grammes.

CASE NO. 42. INDIAN, FEMALE, AGE 27.

This patient had a history of the disease for 6 years. There is no history of previous treatment with hydnocarpus preparations.

Sulphone therapy:

Sulphone treatment was commenced in February 1947 with 1 c.c. of 50% suspension of diamino-diphenyl-sulphone and gradually worked up to 5 c.c. once a week. This dose was maintained until May 1948. From May 1948 to the beginning of July 1948 the patient was placed on rest owing to anæmia. The red cell count dropped to 2.3 millions and the hæmoglobin was 7 grammes. The patient re-commenced treatment in July on 5 c.c. of 25% suspension. After four injections she developed severe lepra reaction and owing to the severity of this sulphone was stopped. Treatment was started again on 16.8.48 with a dose of 5 c.c. once a week and was continued until 19.10.48 when she was advised rest for a period of one month. The blood level did not rise higher than 1.6 mgm%. The bacteriologic index at commencement of treatment was 1. In February 1948 the index deteriorated to 4, but by October 1948 the clinical condition had again improved and the bacteriologic index was again 1.

The total quantity of drug administered up to 19.10.48 was 68 grammes.

CASE NO. 43. FEMALE, AGE 25.

This was a moderately advanced lepromatous case with diffuse erythematous and infiltrated lesions over trunk, extremities and face. The duration of the disease was 6 years. The patient was diagnosed as leprosy by a local physician and then resorted to indigenous treatment. She first sought treatment on 11.11.47.

Sulphone therapy:

From November 1947 to the end of January 1948 she received $1\frac{1}{2}$ c.c. of 50% suspension of sulphone twice a week. This was then raised to 4 c.c.. In February 1948 she had approximately a month's rest owing to the development of anæmia, the blood dropping to 2 million red cells and the hæmoglobin to 5 grammes. She re-commenced treatment at the end of March 1948 when the blood rose to 3 million and the hæmoglobin 9.5 grammes. The dose was gradually increased to 5 c.c. and she continued until the end of May, when she had another six week's rest, the hæmoglobin having dropped to 8.5 but the red cell count remained at 3 million. In August 1948 the red cell count was 3.9 million and the hæmoglobin 12.75 grammes. She continued until the end of September on 5 c.c. 50% suspension, when in October she was given 5 c.c. twice a week of 25% suspension. In October she complained of fever and headache and was given rest. Her hæmoglobin had again dropped to 8. The blood level varied between 0.7 and 1.9 mgm% during the course of treatment. Clinical improvement was steady and satisfactory except during a period of increase of signs in February when the bacteriologic index rose to 4. In October 1948, when she stopped treatment, her index had fallen to 2. She is still under a period of rest.

The total dosage to the end of October is approximately 72 grammes.

CASE NO. 44.¹ ANGLO-INDIAN, MALE, AGE 28.

This patient first presented himself at the Clinic in 1940 when his case was diagnosed as atypical lepromatous. He was given intensive treatment and improved satisfactorily. He however absented himself from treatment for about four and a half years and re-commenced treatment in February 1946 with clinical signs suggestive of leproma. The section indicated that this case was now a lepromatous one. Clinically he showed diffuse infiltrations of the ears and cheeks and poorly defined erythematous and slightly infiltrated macules over the front and extremities. The right ulnar nerve was thickened and there was some anæsthesia over the lateral aspect of the right hand.

Sulphone therapy:

The patient was commenced on sulphone therapy in December 1947 with a 50% suspension of diamino-diphenyl-sulphone. His treatment was somewhat erratic as he absented himself on several occasions. In August 1948 he showed some cyanosis which subsequently disappeared. The dose of diamino-diphenyl-sulphone was 5 c.c. once a week. In October 1948 he was placed on 25% suspension and given 5 c.c. twice a week. His bacteriologic index when he commenced was 3 and at the end of September 1948 it was 2. Clinically the patient showed much improvement and apart from the cyanosis, particularly of the nail beds and lips, in August 1948, which cleared up, there were no other complications. His blood level varied from 0.7 to 2.0 mgm%.

The total dosage up to the end of October was approximately 40 grammes.

CASE NO. 45. ANGLO-INDIAN, FEMALE, AGE 30.

This patient has had leprosy for over 15 years. She was admitted into the Lady Willingdon Leprosy Sanatorium on 17.4.40 as an atypical case (intermediate). Unfortunately at the time she refused biopsy. She received intensive hydnocarpus treatment and was discharged on 9.12.41. She remained outside the Institution and relapsed after approximately 5 years.

Sulphetrone therapy:

She was placed on sulphetrone in November 1947, commencing with 4 tablets a day, increasing by 2 tablets every other day until 12 tablets were reached. In December 1947 she complained of headache and giddiness and treatment was suspended. In the first week of April she went into severe reaction and was given two months' rest.

Sulphone therapy:

In June 1948 it was decided to place her on sulphone therapy. She was given a 25% suspension in a collapsible tube. (The method of injection was to screw on an adapter to the tube after breaking a cellophane seal, then fix on a needle, insert this into the sub-cutaneous tissue and milk the tube until a dose of approximately 0.75 grammes was given. The tube contained a total dose of 1.5 grammes.) She continued treatment, with one week's rest, from July 1948 until October 1948 without any reactions. The patient looked clinically a moderate leproma with extensive infiltrated lesions and thickening of eyebrows, cheeks and ears. She responded to the treatment well, did not have any further complications and her bacteriologic index, which on commencement of sulphone

therapy (November 1947) was 3, and was still 3 in June 1948, had been reduced two months later (August 1948) to 2. The blood level varied from 0.1 to 0.9 mgm%. Clinically the patient has shown remarkable improvement (vide photographs).

The total dosage was 11 grammes.

CASE NO. 46. INDIAN, MALE, AGE 32.

A moderately early lepromatous case showing diffuse lepromatous lesions with no definite macules, skin infiltrated, ear lobes thickened, ulnar and peroneal nerves enlarged with corresponding anæsthesia. The patient had treatment at the Government Hospital two years previously and during 1947 had eight months' indigenous treatment.

Sulphone therapy:

He was first admitted in July 1948 and placed on sulphone, 25% suspension in collapsible tubes. The dose was approximately 0.75 grammes (i.e. half a tube) and was continued with a fortnight's rest at the end of July until October 1948, when he was given a month's rest. The rest in June was given owing to the development of a cellulitis of the face. He was put on a course of penicillin and sulphadiazine. While the patient has shown no marked clinical improvement (clinical improvement in such cases is difficult to assess), his bacteriological improvement has been rapid and the bacteriologic index has changed from 2 to 1 in four months. His blood level was constantly below 1 mgm%. Apart from the cellulitis which developed and had nothing to do with treatment, he showed no complications.

The total dosage to the end of October 1948 was 3 grammes.

CASE NO. 47. INDIAN, MALE, AGE 27.

This was a case of moderately advanced diffuse leproma with a few nodules on the back and flanks and several nodules on the buttocks. The ear lobes were thickened. The patient had previous treatment from June 1947 and was given injections twice a week, a total of 145 c.c. hydnocarpus oil and 143 c.c. ethyl esters being administered over a period of five months. No appreciable clinical improvement was noted.

Sulphone therapy:

In November 1947 he was placed on sulphone therapy, commencing with bi-weekly injections, 1 c.c. of a 25% suspension of diamino-diphenyl-sulphone and increasing within four months to 7 c.c. He remained on 7 c.c. until June 1948 when it was considered that he probably was receiving too high a dose and this

was reduced to 5 c.c. Between 4.2.48 and 6.3.48 he suffered from reaction and anæmia (blood picture 2.7 millions and hæmoglobin 7.5 grammes). Sulphone was stopped for one month and he was placed on intensive yeast and iron therapy. By 2.3.48 his blood picture had recovered and was 4.3 millions' and his hæmoglobin was 11.9 grammes. He then continued injections of 7 c.c. until 12.5.48, when his blood picture again showed some deterioration—3 millions and 9.8 grammes hæmoglobin—and he received three weeks' rest. He was put on further rest from 12.6.48 to 26.6.48 when he re-commenced on a dose of 5 c.c. On 3.7.48 his red cell count deteriorated further to 2 millions although, curiously enough, his hæmoglobin showed 11.9 grammes. He was given a further month's rest and re-commenced on 20.8.48 at 5 c.c. He was absent for 5 weeks and returned on 20.10.48 when his blood count was found to be 2.7 millions and the hæmoglobin index 8 grammes. He was therefore given rest, with intensive iron and yeast therapy, until the end of the month. During this period the clinical condition very markedly improved and his bacteriologic index, which at commencement of treatment was 3 and after three months rose to 4, had been reduced in October 1948 to 1. Apart from occasional periods of rather intense anæmia, he has shown no other toxic symptoms, although on several occasions his blood sulphone rose to 2 mgm%.

The total dose of sulphone given to the end of October 1948 was approximately 66 grammes.

CASE NO. 48. INDIAN, MALE, AGE 36.

This was an advanced lepromatous case with marked lepromatous infiltrations and nodules especially on the extremities, ears and buttocks. The patient received no hydnocarpus oil injections at the Christian Medical College Hospital, Vellore, although he states that he underwent treatment at the Government Hospital, Madras, and that he improved, but during the past eighteen months the condition became steadily worse and, according to the patient's history, the deterioration was more marked after a course of indigenous treatment.

Sulphone therapy:

He was placed on diamino-diphenyl-sulphone in July 1948 on a dosage of 5 c.c. twice a week. The patient continued without rest until October 1948 when his blood count dropped to 2.6 millions and his hæmoglobin was 6 grammes. The patient is still on rest. His hæmoglobin and red cell count have satisfactorily improved. His clinical condition during this period showed quite

definite improvement although he had obviously lost weight. The bacteriologic index on commencement of sulphone treatment was 4. For a short time in August 1948 this increased to 5 and by the end of October 1948 it had improved and was only 2. Other than anæmia the patient showed no toxic signs. The sulphone blood level at no time rose above 2 mgm%.

The total dose of sulphone given up to the end of October 1948 was 31 grammes.

CASE NO. 49. INDIAN, MALE, AGE 33.

The patient was first diagnosed as a lepromatous case in 1936 and admitted to the Lady Willingdon Leprosy Sanatorium where he remained until 1941. He was then discharged with a quiescent certificate (six months negative). In January 1946 he had definitely relapsed because there was a history of reaction for which he was treated with indigenous remedies. In February 1947 the patient was admitted to the Government Pentland Hospital, Vellore, suffering from lepra reaction and was discharged on April 20th, 1947. At the end of June 1947 he was re-admitted to the Pentland Hospital with reaction and discharged on 7.8.47. Again in December 1947 he returned to the Government Pentland Hospital with reaction. The patient was then a moderately advanced leproma with slight infiltration of face and forehead and at the time of admission rose spot nodules and erythema of the lesions.

Sulphetrone therapy:

On his third admission, in December 1947, he was placed on 25% sulphetrone in arachis oil with 0.5% beeswax, commencing with a dose of 3 c.c. Between December 1947 and January 1948 the dose was gradually increased up to 7 c.c. The patient showed no untoward signs until 1st January when he began to show lepra-reaction. During this period he also showed a marked acute iritis. Sulphetrone injections were continued and by January 14th his temperature returned to normal. On January 22nd the patient began to show fever and by the middle of February the peak of his temperature was 102°. Sulphetrone was continued without interruption and by April 7th his temperature returned to normal. The patient continued on sulphetrone until 12th May 1948 when he was given a rest until 5.6.48. The temperature began to rise on June 10th and there were slight rises of temperature until June 27th when his fever increased. By July 9th the peak of the temperature was 102.4° and by July 16th it had reached 103°. Injections of sulphetrone were continued without any rest until 11th August 1948 when the temperature began to subside. By August 18th

this had returned to normal and the patient was discharged from hospital on 20th September. At his own request he was given six weeks' rest between August 11th and September 29th when he commenced again with sulphetrone injections, 10 c.c. twice a week, and has been on sulphetrone continuously. It was noted, however, that the sulphetrone in oil showed lack of absorption and there were large lumps, one of which was aspirated and contained turbid fluid with a very high concentration of sulphetrone. Owing to lack of absorption the sulphetrone emulsion was stopped and he was placed in July 1948 on 25% sulphetrone in normal saline, 10 c.c. twice a week, and has continued with these injections to date. The blood remained satisfactory, clinical improvement was very marked and the bacteriologic index, which at the commencement was 3, had improved to 1 by October 1948.

An interesting feature of this case was the very severe eye reactions which the patient experienced. He had all the signs on two occasions of acute iritis (muddy cornea, contracted pupil, photophobia), in fact the reaction was so severe that the vision was reduced in the left eye to 6/30. He was treated routinely in the hospital and in February he was sent to the Ophthalmic Department of the Christian Medical College Hospital, Vellore. The report given from there described a rather severe iritis with pain, contracted pupils and posterior synechia. His vision returned to normal with routine treatment for iritis and the only sign of iritis is seen in a few small posterior synechia. The fundus is normal and the disc well defined. Since his reaction, which lasted off and on from February 1948 to August 1948 with one short break, he has had no recurrence of reaction or eye signs in spite of the continuance of sulphetrone.

The total dosage of sulphetrone up to the end of October 1948 was 125 grammes.

CASE NO. 50. INDIAN, MALE, AGE 25.

This was an advanced lepromatous case with nodules on chest, extremities, face and buttocks. He stated that the disease commenced four years ago. The patient had a history of indigenous treatment which resulted in deterioration of his condition. No previous history was given of hydnocarpus treatment.

Sulphetrone therapy:

He commenced 25% aqueous sulphetrone on 24.7.48 with a dose of 5 c.c. twice a week and by 14.8.48 this was increased to 10 c.c. twice a week. He continued treatment throughout with

only one week's absence. By October 1948 he showed some clinical improvement and also his bacteriological index had improved from 5 in August to 3 in October 1948. The patient showed no special signs. The drug was well tolerated and absorbed and the blood picture was satisfactory throughout.

The total dosage of sulphetrone up to the end of October 1948 was approximately 45 grammes.

CASE NO. 51. INDIAN, MALE, AGE 28.

This was a very advanced case of lepromatous leprosy with marked lepromatous infiltrations throughout the body, large breaking down nodules on face, back and buttocks, and ear lobes markedly thickened. The bacteriologic index was 4. There was no previous history of hydnocarpus treatment. He must have had the disease many years but the patient could only give one year's history.

Sulphetrone therapy:

He commenced sulphetrone injections, 25% emulsion in ground nut oil with 0.5% beeswax, on 18.1.48. 7 c.c. twice a week were given from February 1948 until June 5th 1948, when he was given 10 c.c. twice a week. In July 1948 it was noticed that sulphetrone in oil was producing large unabsorbed masses and therefore this was stopped and he was given an aqueous solution of sulphetrone 25%, 10 c.c. twice a week. He continued this until the present date, missing only one injection in August. His clinical condition improved very markedly (see photographs), but while the bacilli showed signs of breaking up into granules, the bacteriological condition did not improve. In February 1948 the index was 4 and in October 1948 it was still 4. It is, however, a fairly common observation that with sulphetrone the clinical condition, particularly in advanced lepromas, frequently improves far in advance of the bacteriological condition. Apart from lumps due to lack of absorption of the drug, there were no other symptoms. The patient tolerated the drug well and the blood picture was satisfactory. At the end of three months the lumps are beginning to be absorbed. On September 10th 1948 the patient's temperature began to rise and by the 27th the peak had risen to 102°. The patient was continued with sulphetrone. At the beginning of November he was given P.A.T. and after four injections his temperature returned to normal and has remained normal to date (18.11.48).

The total dose of sulphetrone given to the end of October 1948 was 110 grammes.

CASE NO. 52. INDIAN, MALE, AGE 39.

This case had a history of 7 years' leprosy. During the six months prior to admission he noticed increase of lesions. He was admitted into the Christian Medical College Hospital, Vellore, in November 1947 with lepra reaction. He was a moderately advanced leproma with slight thickening of ears, erythematous lesions and several infiltrated erythematous patches over the back and chest.

Sulphetrone therapy:

He was placed on 25% emulsion of sulphetrone in arachis oil with 0.5% beeswax in November 1947 on a commencing dose of 3 c.c. weekly, increasing to 7 c.c. by January 1948. His dose in June 1948 was increased to 10 c.c. The patient attended regularly for treatment except for one week's absence in August. He showed no untoward symptoms. His bacteriologic index at commencement of treatment was 2; ten months later it was 1. The blood picture was satisfactory throughout.

The total dosage of sulphetrone to the end of October 1948 was 98 grammes.

NOTE.

It was thought that sulphetrone emulsion might show more marked improvement in the large succulent nodular type of case and a visit of Dr. Kate Young to Madras afforded the opportunity of securing her co-operation in the treatment of two cases in her Institution, both of them very advanced lepromatous cases of the Mongolian race. The history of these cases is as follows: —

CASE NO. 53. FEMALE, AGE 30.

The patient was admitted into the Chandag Leprosy Home on the border of Nepal on 12th February 1947 with a history of nine years' leprosy. The first symptoms noticed were blisters on the knees followed by swelling of the face and ears. Shortly after this, nodules appeared which were first discrete but later coalesced until the present stage of advanced nodular lepromatous leprosy was reached. Two or three years ago the patient started to have marked nasal symptoms and a year ago hoarseness of voice and sore throat. On admission her face was covered with large, flat nodules; she had pendulant ears with obvious nodulation; her nose was depressed; there was a large hole in the septum with marked crusting throughout the mouth; there were lesions on the hard and soft palates with ulceration, having a wash-leather appearance on the base: there was ulceration of the uvula and both fauces; vocal cords were thickened; the epiglottis was nodular and enlarged and

she had nodules on hands, feet and legs, arms and shoulders and lepromatous infiltration throughout the body. The bacteriologic index was 6. After one year there was little change in her condition. If anything the throat lesions had deteriorated.

Sulphetrone therapy:

On 23rd January 1948 she was placed on 25% emulsion of sulphetrone in ground nut oil with 0.5% beeswax, 5 c.c. twice weekly. For the first ten days she had transient fever and slight local reaction. After one week, reaction subsided and the dose was increased to 6 c.c. twice a week. On 20.3.48 she went into lepra-reaction and was given one month's rest. In April 1948 she re-started at a dose of 3 c.c. This was continued to date. Her clinical condition steadily improved throughout, nose lesions showing the most marked improvement. Nodules are slowly flattening. The bacteriologic index showed very marked improvement and on 31.10.48 it was 1.

Up to the end of October 1948 she had received a total dosage of 55 grammes, 25% sulphetrone in arachis oil.

CASE NO. 54. MALE, CHILD, AGE 14. (Son of the above woman.)

This child was admitted into the Chandag Leprosy Home in February 1947 with a history of four years' duration. Disease commenced with an erythematous lesion on the upper lip. Later nodules appeared on face, arms, hands and red infiltrated areas over back, arms and legs. There was crusting in the nose and slight depression of the bridge. There were lesions in the hard and soft palates but no actual ulceration. Under hydnocarpus treatment there was no improvement up to November 1947, when there was slight clinical improvement although the smears remained strongly positive.

Sulphetrone therapy:

He was placed on sulphetrone in January 1948, 25% in arachis oil, commencing with a dosage of 3 c.c. twice weekly for a fortnight. This was then increased to 4 c.c. twice weekly. He continued on this dose until February 25th 1948 when it was reduced to 3 c.c. because of slight fever and local reaction. In March 1948 injections were stopped because of lack of absorption at the site of injection. By this time there was considerable clinical improvement. Two months later he re-commenced after the lumps had become absorbed and continued until 26th May 1948. A dosage of 3 c.c. was given twice weekly. In June he was stopped because of weakness and fever and re-started at the

end of July. There was very marked clinical and bacteriological improvement. The index when sulphetrone was commenced was 5 and by the middle of October 1948 it was 1.

By October 20th 1948 he had received 30 grammes of a 25% solution.

DISCUSSION

From the illustrations it will be seen that whatever sulphone is used, be it diasone and sulphetrone by mouth, be it diamino-diphenyl-sulphone in suspension or sulphetrone in aqueous solution or in suspension, there is uniform clinical improvement in all cases. Tables I and II give a general comparison between the dosage and the rapidity of improvement of patients under sulphone therapy. The basis of comparison is the bacteriologic index. It will be noted that sulphetrone as compared to diasone is apparently more rapid in its action. Four out of the nine cases on sulphetrone in an average period of 18 months have become negative, while out of twenty-five cases with diasone treatment only four have become negative. It is interesting to note, however, that all these four are children who have received adult doses. While only one of the sulphetrone cases who have been on treatment for more than nine months has deteriorated or remained bacteriologically stationary, seven cases under diasone have shown no improvement bacteriologically and two no improvement clinically.

With reference to the comparison of diasone and sulphetrone orally with diamino-diphenyl-sulphone and sulphetrone by parental administration, it is obvious that the dosage required orally is very much greater (ten to twenty times) than by injection.

The evidence accumulated over the past two-and-a-half years confirms the fact that the sulphone remedies are effective in lepromatous leprosy. The statement made by one of us (R.G.C.) at the International Conference at Havana (1948) that the early lepromatous cases under hydnocarpus medication respond as quickly as those under sulphone therapy is confirmed, as seen in Table III which gives the bacteriologic indices and the average number of months that it has taken these cases to become negative. It will be noted that cases with a bacteriologic index of 2 and under have on an average taken between 20 and 24 months to become negative. This compares favourably even with the drug which has the most rapid effect, diamino-diphenyl-sulphone. The average period which this drug has taken to produce a negative result is 16 months. There are, however, two drawbacks to hydnocarpus therapy when adequately applied. The first is the painfulness of intradermal injections. The second is that while a large

number respond to hydnocarpus therapy in the early stages of lepromatous leprosy, more than 50% do not recover within the above period. We believe, however, that the percentage of negatives ultimately with the sulphone preparations would be very much higher. This, therefore, is a point in favour of using the sulphone therapy in all lepromatous cases. When, however, a careful analysis of cases is taken, the high dosages of diasone and sulphetrone (an average of 1,900 tablets in the case of diasone and 6,000 tablets in the case of sulphetrone)—as compared with approximately 90 grammes of sulphone by injection, indicates that, other things being equal, injection of sulphone remedies is the method of choice. It is obvious that twice-weekly injections would be much more convenient and much more economical than large dosages by mouth. On these premises alone, therefore, the method of choice should be sulphone by injection. In considering this question, two other factors have to be taken into account—namely, the toxicity of the remedy and the blood concentration of the drug. With reference to toxicity, this will be considered under the separate derivatives:—

(1) *Diasone*. We have had no signs of immediate intolerance as have been described by other workers—for instance, nausea, vomiting or haematuria—but a few cases have shown some deterioration in the blood picture. This has usually righted itself without yeast and iron therapy. There is a general tendency (this observation has been noted by other workers) for the blood picture to improve after six months or so under diasone treatment. As has been pointed out by one of us (R.G.C.), diasone tends to produce lepra reaction in a certain number of cases, approximately 30%. In our earlier cases, not here reported, two cases had to stop the drug owing to the severity of the reaction. It was interesting to note that the liability to reaction continues until some 700—1,000 tablets have been taken, after which the likelihood of reaction is very much less, for the proportion of cases showing severe reaction after 1,000 tablets is very small.

(2) *Sulphetrone*. In the case of sulphetrone the toxic signs were limited to three main ones.—(a) anaemia, (b) severe occipital headache, (c) cyanosis. As has been pointed out by previous workers, the cyanosis produced by sulphetrone is of no practical consequence although one of our cases developed a plum-coloured complexion. This disappeared on continuance of the drug. Another sign of intolerance of the drug is a very severe occipital headache. It is unassociated with high blood levels and disappears on withholding the drug. There seems to be a somewhat greater

tendency for anaemia to develop with sulphetrone than with diasone, but this readily recovers if the drug is withheld and iron and yeast are administered in adequate dosages. We have always taken care that patients on sulphetrone do not become constipated, for it is believed that constipation tends to produce increased blood concentration owing to the fact that the drug is accumulating in the gut and is retained if the bowels are not kept open.

(3) *Diamino-diphenyl-sulphone*. We have accumulated clinical evidence that diamino-diphenyl-sulphone in a 25% suspension of ground nut oil is probably the most potent anti leprosy remedy we have. In several instances there has been an improvement of the bacteriologic index, and in some cases this has been quite striking. We however have found that apart from the reactions which are produced, when the remedy is continuously administered there are certain toxic signs, some of which are serious. These toxic signs are:—(a) anaemia, (b) giddiness, nausea, vomiting, (c) signs of peripheral neuritis as evidenced by pain, particularly along the larger nerve trunks—ulnar and peroneal—and associated with painful limbs and muscles. While sulphone remedies have been stated to have a dangerous toxic effect on nerves, particularly the optic nerve producing optic atrophy, we have had no evidence of permanent damage either to the peripheral nerves or to the special nerve endings such as those going to the retina. The anaemia which is produced on administration of sulphone is sometimes very alarming. In one case the blood dropped to 2.2. millions with a haemoglobin of 6 grammes, but with the discontinuance of sulphone and the administration of iron and yeast within 14-21 days the blood picture had returned to almost normal. One serious symptom is the tendency of this drug to produce signs of liver toxicity. These are nausea, vomiting, hepatic pain and jaundice. All our cases have recovered but we have had no means of assessing the amount of liver damage. Until a dosage is devised which can be guaranteed not to produce these toxic signs it is impossible to contemplate the administration of diamino-diphenyl-sulphone on a large scale. It is of interest to note that Molesworth (personal communication) has stated that a smaller dosage, even as small as 1 gramme per week, appears to be effective in lepromatous leprosy. It is to be remembered that the florid type of leproma responds more dramatically than the slowly progressive lesion, which seems to take a longer time to effect the same clinical improvement. An excellent illustration of this fact is seen in cases from Dr. Kate Young's institution who have shown dramatic bacteriological improvement and all these cases belong to the Mongolian racial

group. It may be, therefore, that a dosage of 1 gramme or 1.5 grammes per week is sufficient to maintain blood levels for effective therapeutic results. In this connection it might be stated that one series of cases had sulphone administered to them by means of a collapsible tube. This method of injection was suggested by a visit the senior author made to the laboratories at Wilmslow where it was used in mastitis of cows. Instead of a canula, the collapsible tube is fitted with a needle which is screwed on after breaking the cellophane covering. The needle is inserted into the sub-cutaneous tissues and the suspension slowly "milked" into the tissues. The collapsible tube can be charged with the dosage required, which would normally be about 1 gramme. If the toxicity of diamino-diphenyl-sulphone can be overcome, this method of injection (vide illustration 20) will be of great value, for instead of having to sterilise all the component parts of a syringe, the only parts that need sterilisation are the adapter and the needle.

We believe that diamino-diphenyl-sulphone can be administered provided a dosage of not more than 1.5 grammes per week is used and that a month's rest is given every 2—3 months. Further the blood concentration should not be allowed to rise above 2 mgm%.

(4) *Sulphetrone (by injection)*. Sulphetrone has been given by us parentally in the form of a 50% aqueous solution and a 25% emulsion. We have commenced injections of 25% aqueous solution. These drugs (vide illustrations) are effective in comparatively small doses, namely 14 c.c. (7 c.c. twice a week). We are hoping, however, to be able to reduce the dosage as in the case of diamino-diphenyl-sulphone. In the case of sulphetrone we believe that much smaller dosages are effective.

(5) GENERAL OBSERVATIONS.

(a) *Tissue concentration*. It seems to be anomalous that a dose of approximately 4-7 grammes of sulphetrone and 1-2 grammes of sulphone a week is as effective as 6 grammes of sulphetrone by mouth per day. The reason for this effectiveness we believe is due to the ability of the tissues to fix the drug. In experimental sulphone therapy on animals we have found appreciable quantities of sulphone in all the organs of the body—the spleen, the liver, the kidney, the bone marrow—and therefore, if there is an affinity of the tissues for sulphone and sulphetrone it appears reasonable to assume that injections parentally will be effective. In connection with the estimation of diamino-diphenyl-sulphone and sulphetrone in the skin, the earlier work showed that we were in error in our conclusions owing to the fact that the anaesthetic that we

used produced a colour reaction and therefore made our reading inaccurate and very varied. On the introduction of cocaine suggested by the I.C.I. Laboratories, the fallacy of a colour reaction produced by the anaesthetic has been overcome and our work on skin concentrations is being repeated. The following conclusions seem reasonable to draw.—(i) the sulphones—using this word in the generic sense—are effective in lepromatous leprosy; (ii) parental administration is more economical and cheaper than oral administration; (iii) parental administration of sulphetrone gives rise to no deterioration in the blood picture; (iv) until a safer dosage of diamino-diphenyl-sulphone is worked out we believe that it is reasonable to recommend for the routine treatment of leprosy, particularly for those cases which do not respond to hydnocarpus treatment or which have relapsed, sub-cutaneous injections of 50% sulphetrone in water in a dosage of 7 c.c. twice a week.

(b) *Morphological changes in the M. leprae.* The general observation is that under sulphone therapy the bacilli undergo certain morphological changes. The bacilli first become beaded and then granular forms appear. Ultimately, the majority of bacilli in a slide are mostly granular, even though there is very little difference in the bacillary content of the slide. For instance, in illustrations 1-3 and 11-12 six months had elapsed between treatment and, while there was marked clinical improvement, the bacteriologic index remained the same. Later, the bacilli began to diminish in numbers and ultimately, only acid fast dust was seen. It is impossible as yet to conclude that the fragmentation of the bacilli means death, for this fragmentation, although not so marked, is seen with hydnocarpus treatment and probably the fragmented and granular forms indicate that the conditions under which the bacilli are living are unfavourable. Further proof that the fragmented and granular forms may not be dead bacilli has come to us recently. Case No. 30, which over a period of almost two years showed a steady clinical and bacteriological improvement up to October 1948 (the bacteriologic index was reduced from 4 in November 1946 to 2 in October 1948), with very little warning suddenly began to show increased symptoms and fresh sub-cutaneous nodules appeared, chiefly on the outer extremities of the arms. Smear examination showed that the bacteriologic index had increased to 3 and there had been obvious increase in the bacillary content and there were several globi in fields examined, all the bacilli being granular. Time remains to show whether there will be a further increase or whether these bacilli will be dealt with and the case ultimately become negative.

(c) *Reactions and the discontinuance of sulphone therapy.* Another matter which deserves discussion is the question of rest periods. Because we assume that the sulphones—using this term in the generic sense—are chemo-therapeutic agents, we believe that rest periods should only be permitted when there are definite signs of intolerance. For diasone this is shown in the form of a secondary anaemia. With diamino-diphenyl-sulphone suspension, anaemia is liable to occur and toxic symptoms, which have already been described, would indicate withholding the drug. For sulphetrone, the only two symptoms which need to be noted are (i) anaemia and (ii) persistent occipital headache. We are of the opinion that every case probably passes through a stage when there is some exacerbation of the disease, either shown by slight lepra reaction or temporary increase of the bacteriologic index or in more severe lepra reaction sometimes of the nature of erythema nodosum leprosum, recently described by Woolcott, Johansen *et al.* The latter condition is a very interesting one which in our opinion is simply one of acute lepra reaction. Sometimes it is so severe that the temperature rises to 104, 105 and even 106° and under these conditions the remedy has of course to be stopped. We believe, however, that unless the fever is very high, continuance of the sulphone remedies is indicated. Figures 16-19 indicate a temperature chart during a reaction under sulphetrone which subsequently subsided in spite of continuation of the drug. In this connection it may be noted that one of the signs of reaction which is relatively frequent is that of iritis. Sometimes, as in Case No. 49, this is very severe and the vision may be reduced to almost nil. While the symptom can be extremely alarming, we believe that general principles should be followed and that the drug should be continued. At the same time active measures should be taken to combat the iritis and to dilate the pupil. It is remarkable how a very severe iritis will recover under sulphone therapy with practically no deterioration of vision. We have already mentioned that there is evidence that cases under diasone therapy tend to react during the early stages and after they have been given over 1,000 tablets reaction tends to be either very much less severe or cease altogether. We believe that this reaction phase cannot be avoided and there is no point in stopping the drug or reducing the dose because as the dose increases and the blood concentration either rises to its former level or the drug acts for a more prolonged time, the patient will pass out of the reaction phase.

(d) *Absorption of the drug.* While it seems preferable that the drug should be exhibited in an oily medium, there have been certain

disadvantages particularly in connection with the injection of emulsions of sulphetrone in oil. This has been evidenced in a large number of cases (25%) which have shown areas of lack of absorption. These masses have continued in some cases for several months and on aspiration have been found to contain a high concentration of sulphetrone. Until, therefore, this problem, which is essentially a pharmaceutical one, is overcome, any sulphone in an oily medium which gives lack of absorption cannot be recommended. The parent substance, diamino-diphenyl-sulphone, in a suspension of arachis oil and of hydnocarpus oil has not generally shown these drawbacks.

(6) *Conclusion.* In conclusion, therefore, it is evident that all the sulphones have a definite action on the M. leprae and the choice of the sulphone depends on three factors:—(i) price, (ii) ease of administration, (iii) availability and absence of toxic effects or lack of absorption. Viewed in this light the preference at present must be given to a 50% solution of sulphetrone in water. In view of the fact, however, that the oily medium may be more slowly absorbed, it would seem that work should be carried out on the production of an emulsion or a suspension which would be easily absorbed. Diamino-diphenyl-sulphone, in our opinion, is the most effective anti-leprosy remedy which we have used, but until the question of toxicity is settled it is not at present advisable to use it.

(7) *Acknowledgment.* Finally, I should like to acknowledge the help of the Bio-Chemistry Department of the Christian Medical College, Vellore and the staff of the Lady Willingdon Leprosy Sanatorium and the Silver Jubilee Children's Clinic, Madras. Appreciation of the help of Miss Marcroft in arranging and collecting the material for presentation is recorded. The work has been made possible as a result of generous supplies of the necessary drugs from Imperial Chemical Industries, Burroughs Wellcome and Abbott & Co., and we are indebted to May & Baker, Ltd., who have placed funds at our disposal which have enabled the work to be continued along bio-chemical and other lines.

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* I am indebted to the article by Sharpe and Payne for these references.

TABLE I

COMPARATIVE TABLE OF CASES WHICH HAVE BECOME NEGATIVE UNDER SULPHONE THERAPY.

Drug used	Total No. of cases	No. of cases negative	Average period to become negative	Average total dose
Diasone	25	4	26 months	677 gms.
Oral Sulphetrone	9	4	18 „	3165 „
Sulphone (Diamino-diphenyl- sulphone)	11	2	16 „	90 „
Sulphetrone by injection ...	6	—	—	—

TABLE II

COMPARATIVE TABLE OF CASES WHICH HAVE NOT BECOME NEGATIVE UNDER SULPHONE THERAPY.

Drug used	Total No. of cases	No. of cases improved		No. of cases stationary		No. of cases worse		Average period under treatment	Average total dose
		Clinically	Bacterio- logically	Clinically	Bacterio- logically	Clinically	Bacterio- logically		
Diasone	25	19	14	2	7	—	—	19 months	618 gms.
Oral Sulphetrone	9	5	4	—	1	—	—	22 „	3096 „
Sulphone (Diamino- diphenyl-sulphone) ...	11	8	7	1	2	—	—	11 „	34 „
Sulphetrone by injection	6	6	5	—	1	—	—	8 „	81 „

TABLE III

PATIENTS UNDER HYDNOCARPUS TREATMENT DISCHARGED AS NEGATIVE BETWEEN 1938 AND 1947.

Year	Total No. of patients discharged negative	Average period of treatment (in months) to become negative								Average Maximum weekly dose (c.c.) H. oil Esters	
		Early (B. Index 0—1)		Moderate (B. Index 2—3)		Advanced (B. Index 3—4)		Highly advanced (B. Index above 4)			
		No. of pts. in group	Time to become negative	No. of pts. in group	Time to become negative	No. of pts. in group	Time to become negative	No. of pts. in group	Time to become negative		
1938	74	18	11	6	12	17	29	33	53	10.5	2.8
1939	74	14	11	18	22	16	43	26	63	8.7	3.7
1940	77	28	14	20	22	12	38	17	72	10.2	3.7
1941	95	35	16	25	22	22	38	13	52	9.2	3.4
1942	133	44	18	32	25	38	43	19	53	9.3	3.9
1943	39	19	15	16	25	2	47	2	84	6.7	3.8
1944	75	43	24	23	34	9	48	—	—	6.9	4.4
1945	46	28	21	12	36	6	49	—	—	5.8	5.5
1946	69	39	25	25	33	5	54	—	—	6.3	5.6
1947	127	80	23	40	35	6	60	1	104	6.2	7.8

NOTE.—The average period taken for cases which have become negative under hydnocarpus therapy with an index of 0—1 over the past ten years was 20 months, with an index of 2—3 it was 24 months, with an index of 3—4 it was 42 months and with an index above 4 it was 60 months.