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EDITORIAL.

CHAULMOOGRA TREATMENT OF LEPROSY.

From time immemorial chaulmoogra (now more often called hydnocarpus) oil has been reputed for its beneficial results in the treatment of leprosy. For hundreds of years the oil has been administered orally in India and the powdered seeds have long been given by the Chinese. Since 1909 the esters of chaulmoogra and other preparations as well as the oil itself have been given by injection. Many forms of treatment for leprosy have come and gone, but leprologists have always returned to chaulmoogra as the one drug which gave definite results.

Is this reputation justifiable? If this is doubtful how can the matter be settled definitely?

G. W. McCoy, formerly Medical Director, United States Public Health Service, writing on this subject in 1942* recalls how 25 years ago he had concluded from the study of 16 cases 'that the oil is helpful in cases—perhaps the majority.'

review of this experience . . . after 25 years have elapsed leaves him with the opinion that not enough consideration was given to the natural evolution of leprosy

to improve spontaneously, and to the extreme meagreness of the data, which were insufficient for even the modest conclusion that was drawn! After a quarter of a century he is left 'with the very definite impression that chaulmoogra oil and its derivatives are of doubtful value in the treatment of leprosy.'

McCoy quotes four leprologists who make the following comments respectively: 'In lieu of anything better to offer we deem it necessary to use it.' 'Chaulmoogra oil and its derivatives have not been shown to be of specific value in the treatment of leprosy . . . patients have shown equal improvement under the administration of other oils and esters.' 'In a small percentage it appears to have been of value.' 'I have never noted any unquestionable evidence that ethyl chaulmoograte is of any value in the treatment of leprosy.'

On the other hand, the resolution adopted at the International Leprosy Congress in 1938 stated: 'Hydnocarpus oil and its esters, administered intramuscularly, subcutaneously and intradermally, remain, so far as our present knowledge goes, the most efficacious drugs for the special treatment of leprosy.'

committal phraseology, for the most efficacious may not be able to effect much.

Still there is no doubt that differences of opinion exist among experienced clinicians working in various countries; can we account for these differences?

It is an accepted fact that the resistance of the majority of people to leprosy is high, while that of a small minority is low. In an endemic country individuals in each of these groups are liable to be exposed to infection. Under such exposure subjects with low resistance are more likely to contract leprosy, and leprosy of a severer type, than those with high resistance. Also, the more promiscuous and unhygienic a community is the greater will be the average exposure to infection of the average individual, and the greater the number of cases of leprosy that will occur among the higher resistance group; but the majority of those affected will suffer from the milder type of leprosy, which progresses slowly, is limited in extent and shows a tendency to self-cure. In such a community the lepromatous type rate would be low in proportion to the total cases and in proportion to the tuberculoid type rate.

A doctor working in such an area would be likely to get good results with treatment, as the high resistance of the majority of his patients would help towards recovery. On the other hand, in an endemic community with a better standard of hygiene and whose individuals were more careful to avoid infection, though the total cases of leprosy would be fewer, the lepromatous type rate would be higher and the recovery rate under similar treatment would therefore presumably be lower.

This explanation would at least partly account for the difference in results obtained with chaulmoogra treatment in various countries.

As far as we are aware no really satisfactory test of the efficacy of chaulmoogra in leprosy has yet been carried out. Where it has been attempted the selection of cases has been on a clinical and bacteriological basis. Lepromatous cases have not been distinguished from those with severe (major) tuberculoid lesions. But we now know that the prognosis in the latter is very much more favourable than in the former, and any confusion between the two is bound to vitiate the results. Also there is the limbo of indeterminate cases which are difficult to type on a clinico-bacteriological basis alone as this may fail to give a clear indication of resistance and therefore of prognosis.

Histological examination is often useful in classifying doubtful cases, but we should not rely too much on cytological appearances in making a prognosis.

The most dependable standard of the patient's resistance yet available is the lepromin test, and it is essential in selecting cases

for a reliable therapeutic experiment to combine this test with the clinical and bacteriological examination in order to assess the chance of spontaneous recovery without treatment.

Cases should be selected in which the lepromin test has been found consistently negative at two monthly intervals over a period of at least six months ,and in which both clinical and bacteriological examination have shown that they are of the lepromatous type. Cases with complications such as septic infection and other debilitating conditions should be excluded, and only fairly early uncomplicated cases retained.

As the trial would have to continue over a period of at least two years much would depend on the intellectual and emotional attitude of the patients, on their intelligence, cheerfulness, determination and persistence. That being so it might be difficult to arrange satisfactory controls, and evaluation of improvement might have to be determined without this means of checking the results.

The estimation of results must depend chiefly on a combination of clinical and bacteriological examinations. Clinical signs alone are deceptive, as the subsidence of a temporary reaction, or the supervention of some weakening condition may cause flattening out of lesions and give a false temporary appearance of improvement not confirmed by bacteriological examination. Even when on such examination the case becomes almost or entirely negative, prolonged observation is necessary to ensure that the improvement is permanent.

The most satisfactory confirmation of improvement is when the lepromin test, at first negative, becomes definitely and permanently positive, but this appears to be a very rare occurrence.

Such a trial if carried out as described above would help to establish or demolish the title of chaulmoogra to a specific effect in leprosy, and the test would be even more satisfactory if closely corresponding control cases could be treated at the same time with a bland preparation such as olive oil having slight irritant properties, similar to those of the chaulmoogra oil or derivative used.

It is well known that the intradermal method of injecting chaulmoogra has a marked effect in clearing up chronic tuberculoid lesions. Leprides, which have persisted for months or years without change, or with only slow growth, often disappear rapidly after one or more intradermal infiltrations. But there is no reason to believe that this is due to anything but a mechanical effect and similar results may be obtained by substituting other oils with equal irritating properties. In carrying out the experiment

described above it would therefore be advisable to inject the drug intramuscularly or subcutaneously, as the intradermal route might vitiate the test by its mechanical local effect on lesions.

The chance of being able to carry on this experiment without interruption for as long a period as two years would largely depend on the results obtained. If these were really favourable the patients would find interest and encouragement to persist. If, on the other hand, they failed to make definite sustained progress, they would be likely to become discouraged and give up before this period had elapsed, and their doing so might fairly be taken as an indication of want of success.

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*Chaulmoogra Oil in the Treatment of Leprosy (1942) Public Health Reports, **57**, 1727.

ATLAS OF LEPROSY.

By D. C. DANIELSSEN and C. W. BOECK.

This atlas was first published along with their treatise on leprosy by the authors in 1847. The orginal was in Norwegian, but a French edition was published the next year. The original atlas was in colour; the present edition is in black and white, there being twenty-four beautifully reproduced large plates with clinical and pathological illustrations.

Every doctor interested in leprosy should have a copy of this famous atlas, and it should certainly be on the shelves of all medical libraries.

Dr. H. C. de Souza-Araujo, of the Institute Oswaldo Cruz, Rio de Janeiro, has celebrated the Centenary of this famous work by re-editing the French edition in honour of the authors who were the founders of modern leprosy. He has generously asked that the profits from the sale be devoted to the International Leprosy Association and the reorganisation of the *International Journal of Leprosy*, published for many years in Manila. He asks that the price of copies ordered from him in Brazil should be forwarded to the Secretary-Treasurer of the International Leprosy Association, 167 Victoria Street, London, S.W.1. The price named is cheap: $4.00 or £1.

SOME OBSERVATIONS ON THE ROLE OF ALLERGY IN LEPROSY (2).

PART II.—ALLERGY AND THE MACULAR SERIES.

T. F. DAVEY.

It is customary to describe three varieties of leprous macule. The Cairo Conference (1938) contented itself with two, recognising (a) Simple Macular (with flat macules), and (b) Tuberculoid Macular (with major and minor subtypes), subvarieties of neural leprosy, but admitting that the term, Macule, "is sometimes used to designate lepromatous patches." Lowe, (1936) and Rogers and Muir (1946) all describe and illustrate a lepromatous form of macule sufficiently distinct to merit separate classification.

Macules are the commonest feature of leprosy in Nigeria. Their great diversity, while clearly indicating their immunological importance, is at the same time an obstacle to their effective classification. An understanding of their role in the natural history of the disease and their consequent classification is eminently desirable, for macules undoubtedly form the link between the immune individual on the one hand, in whom no visible disease appears, and the highly susceptible person on the other hand, who exhibits anergic lepromatous leprosy. The three recognised varieties, (a) lepromatous, (b) simple neural (flat) macules, and (c) tuberculoid macules, do not provide an acceptable classification of macular leprosy for at least two reasons. In the first place, the distinction made between tuberculoid macules and simple neural flat macules is unsound, for it throws the emphasis on the degree of thickening and elevation of a macule as its distinguishing feature. All types of macule represent a localised reaction to the lepra bacillus in the skin, the effectiveness of which is to be measured not by the degree of thickening and elevation in the macule, but rather by the success with which the bacillus is localised and destroyed. This may certainly occur effectively in a flat macule. Wade, (1937) and Ermakova, (1939) have clearly demonstrated by extensive histological studies that pale flat macules are in many cases intimately related to clinically tuberculoid macules, the difference being one of degree only. In such cases the disease is confined mainly to the papillary layer of the corium, and though epithelioid cells rarely form actual tubercles, their presence conclusively indicates the allergic nature of the response, and its unity with that occurring in tuberculoid macules.

It has been pointed out in Part I (Davey 1946) that the allergic tuberculoid response may be effective over a considerable range of intensity. The minor tuberculoid macule may in appropriate circumstances represent as effective a response as does the more violent major tuberculoid response. In the same way the even milder response which appears to the naked eye as a flat macule may be adequate in favourable circumstances.

An even more fundamental weakness in the triple classification is its inadequacy. Although in their typical form the three varieties represent readily identifiable types of macule, deviations from type are so numerous in clinical practice that it is impossible to place all macules in these three compartments without broadening the description of each to such an extent that much of their value is lost. There are more than three types of leprous macule, and the three standard varieties cannot therefore embrace them.

THE MACULAR SERIES.

If the macule indicates a reaction to the bacillus designed to localise and destroy it, the only reasonable criterion for classifying macules of varying appearance is the degree of success with which this fulfils its function. The thickening of the skin in the macule is a secondary consideration, as is also the number of bacilli found on a single examination. What matters is the speed with which the bacilli are destroyed, the sterilising power of the response. If a sufficiently large number of cases of macular leprosy is examined and observed over a period, it is possible to arrange the various macular forms in descending order of effectiveness, and if this is done it is apparent that they do not fall into a few, well defined groups, but rather form a continuous series. At one end of the scale are seen the effective, highly localising macules typical of the most advantageous types of tuberculoid and pale flat macule. At the other end are seen the innumerable poorly defined macules of the least satisfactory lepromatous group in which there is no effective localisation and the macules represent a temporary phase in the advance of the infection. Between these two extremes are seen macular forms, through the increasing deviations of which the gulf between the two extremes is effectively bridged and a continuous series produced with no distinct break at any point. Before discussing the implications of this series, it is perhaps desirable to describe it in greater detail.

(a) *The Optimal Allergic Group.*

The two extremes of the series are well defined. At the

most effective end of the scale are placed macules, clinically tuberculoid or simple neural, having the following characteristics.

1. The number single or multiple.
2. Sharp definition of the edge, only consistent with a relatively slow rate of spread.
3. Rapid destruction of bacilli in the lesion to produce a negative bacteriological test.
4. Spontaneous resolution, which may occur simultaneously through the lesion, but more commonly appears as a spreading zone of healing in the centre of the macule.
5. Hypopigmentation of varying degree in dark skins, which may or may not be associated with erythema.
6. Interference with local nerve function, leading to loss of sensation in the macule.
7. A positive lepromin test.

These characteristics may be seen in macules of all degrees of thickening and elevation, and all macules exhibiting them, whether they are raised or flat, should be grouped together into a single optimal allergic group.

Among these characteristics, rapid destruction of bacilli is the most fundamental, but is difficult to demonstrate in its later stages, as a persistently negative bacteriological test is still consistent with a macule which continues to spread. The standard bacteriological test is a gross method of investigation. Spontaneous resolution is perhaps the feature of greatest practical value, and no case should be classified in this group unless it is in evidence. Loss of nerve function in the skin of the macule is generally believed to be the mechanical result of the cellular reaction in the cutaneous nerve, caused by ascending infection. Some infections are more neurophilic than others, but in general the degree of nerve involvement runs more or less parallel with the intensity of the response, being most pronounced in major tuberculoid lesions. A certain amount of time is required for pressure effects to manifest themselves, so that sensation may be normal in the early stages of macules. Loss of thermal sensation, of light touch, and sensibility to pain usually advance in that order. Loss of sensation is frequently absent in macules on the face. Loss of nerve function is thus not an invariable accompaniment of macules in this group.

Within the optimal allergic group, the most advantageous form of macule is undoubtedly the single tuberculoid macule, and this in many instances represents a purely localised infection,

destined to be controlled and eliminated. In abortive infections this local lesion may be small and insignificant, and not recognised as leprosy by the patient. Subclinical cases of this type are frequently seen on leprosy surveys among the contacts of more advanced cases.

(b) *Lepromatous Macules.*

At the opposite end of the scale are found lepromatous macules, which stand in sharp contrast to macules of the optimal allergic group, and have the following characteristics.

1. They are usually extremely numerous and, if few when first seen, are liable to multiply and become numerous.
2. The edge is poorly defined and macules rapidly spread and coalesce, often to the point of covering the entire body surface.
3. Bacilli are numerous and persistent in the macules, and the skin elsewhere is frequently bacteriologically positive.
4. There is no sign of spontaneous resolution in the centre of macules.
5. Hypopigmentation and erythema are present in varying degree.
6. Nerve involvement is either slight or entirely absent.
7. The lepromin test in normal skin is usually negative.

This group is only one step removed from the diffuse infiltrating and nodular forms of leproma, but is distinguished from these forms by the presence of hypopigmentation combined with the focal arrangement of the lesions. Nodular and diffuse lepromatous leprosy may exist even in an advanced state without any sign whatever of hypopigmentation in the form of macules, though in its later stages there is occasionally seen a vague diffuse pallor, not localised into the form of macules. Lepromatous macules appear at a much earlier stage than this, and are sometimes described as, " Prelepromatous." This is only part of the truth. Sometimes such macules spread and coalesce to form extensive pale areas in which the disease advances to become diffuse leproma, and if the entire body surface is involved, the patient may be thought to be merely a pale skinned individual suffering from uncomplicated anergic lepromatous leprosy, the macular phase being entirely masked. Before this stage is reached, diminishing islands of darker skin, frequently most persistent in the groins, indicate the macular origin of the hypopigmentation. The writer has described a case of this type (Davey, 1942).

Although the advance of lepromatous macules to diffuse leproma is common, it is by no means invariable. The two types not infrequently coexist in the same patient, but we have seen cases in which the progress of the disease in the macular areas has been halted, both before and after the point where widespread coalescence is followed by a long stationary phase of the disease, with no advance to graver forms, but a gradual decline in the concentration of bacilli in the skin. This welcome state of affairs is only very rarely seen in true anergic diffuse leproma, and even then is only likely in the later stages of the disease, by which time the nose, larynx and testicles have usually become affected.

Lepromatous macules thus represent a slightly more advantageous form of the disease than true diffuse leproma, and though the advantage may be temporary, it does represent a feeble attempt at localisation in the skin, and is thus distinct from true anergic leprosy.

(c) *Intermediate forms.*

Within the two extreme forms there are many intermediate varieties of macule. Working along the series from the optimal group, the first unsatisfactory deviation is displayed by macules. clinically of tuberculoid or simple neural type, but in which spontaneous resolution is delayed or lacking, the macule taking a very chronic course. In the next deviation, deficiency in spontaneous resolution is accompanied by a lack of sharp definition in the edge of the macule. "Streaming" edges are seen, and there is a tendency for adjacent macules to meet and coalesce without this being succeeded by resolution. As these deviations become increasingly pronounced, the number of macules present tends to increase, and further along the series they are usually numerous. At the same time, signs of nerve involvement diminish. We thus arrive at a group exhibiting numerous macules in which there is defective resolution, which have a fairly well defined edge but tend to coalesce, which exhibit only slight signs of nerve involvement, yet remain persistently bacteriologically negative. They thus lie in an intermediate position between the extreme forms. Macules of this type are common in Nigeria, and both flat and raised forms exist. A distinct variety takes the form of innumerable papules which spread and flatten to form small hypopigmented macules which then proceed to coalesce, the bacteriological test remaining negative. The Cairo classification makes no provision for a case of this sort. From these intermediate cases it is a short step to macules resembling lepromatous macules, yet still persistently bacteriologically negative, until

through similar lesions with increasing bacillary content we finally arrive at typical lepromatous macules.

Reviewing the series as a whole, there is seen a progressive loss of definition and resolution in macules towards the lepromatous end, accompanied by an increase in the persistent bacillary content. Features common to all types of macules are hypopigmentation and erythema, both of which are variable. Sensory changes in the macule also decline and disappear towards the lepromatous end, though they may still be in evidence apart from macules.

The macular series can be traced most perfectly where the macules are flat or of mild elevation. Nevertheless it is of interest to note that unfavourable deviations occur even with major tuberculoid macules. Cases of this type have been described by Wade (1940).

IMPLICATIONS OF THE MACULAR SERIES.

The very existence of the macular series has important implications. The absence of any distinct break in it indicates that the difference between one form and another is not due to fundamentally distinct disease processes, but is quantitative rather than qualitative, produced by varying degrees of the same factors, rather than entirely different factors. In other words, that although appearances differ, there is a common thread running through the entire series and binding one member to the next. It is generally recognised that tuberculoid leprosy has an allergic basis, and the clinical appearance of the tuberculoid macule is therefore the resultant of three varying factors, (a) antigen concentration, (b) local antibody production, and (c) the allergic cellular reaction to the antigen-antibody complex. It is reasonable to consider the entire series as produced by the interplay of these same factors in varying intensity, increasingly unsatisfactory forms of macule being manifest as the local allergic defence mechanism declines in effectiveness in relation to antigen concentration. If this is the case, we are witnessing along the macular series the progressive failure of the allergic response, from optimal at the tuberculoid end, to transitory and ineffective at the lepromatous end.

There is considerable evidence, both clinical and experimental, to support the conclusion that an allergic mechanism underlies all macular forms of leprosy, whatever other factors may be involved. From the clinical standpoint, (a) it is difficult to explain the sudden appearance of a crop of macules apart from allergy. Such a crop is a very common occurrence and the macules may conform not only to the optimal group, but to any

point in the macular series. (b) The sudden appearance of a macule ½ inch or more in diameter is best explained on a basis of allergy. (c) The existence of the macular series itself is best explained in the same way. From the experimental point of view, two methods of investigation are open to us, (a) histological studies, (b) the lepromin test. At the present time, thorough histological studies have been made only of the optimal group of macules, and studies of the intermediate forms and the lepromatous group are inadequate for judgments to be made. The lepromin test forms a simple and ready means of investigation, and has been applied to macules of various types.

THE LEPROMIN TEST AND THE MACULAR SERIES.

A positive lepromin test in an infected person indicates the existence of allergic hypersensitiveness to the antigens of the lepra bacillus. A positive test is a commonplace in tuberculoid leprosy, but in order to investigate the status of other macular forms we have applied the test to some hundreds of patients among whom all varieties of macular leprosy are represented. In view of the important local aspect of allergy in leprosy, discussed in Part I, and in order to discover the allergic state of macules, the test has been carried out in the macules themselves as well as in normal skin.

For the purposes of this work, three types of lepromin were used, (a) crude lepromin prepared locally by the method described by Rogers and Muir (1940), (b) partially purified lepromin prepared locally, following the earlier stages of Dharmendra's technique (1941), (c) samples of Dharmendra's purified lepromin kindly supplied by the courtesy of Dr. E. Muir.

It was first necessary to compare the three types of lepromin used. For this purpose, 14 patients were selected, all exhibiting tuberculoid macules in a state of activity. Adjacent or comparable macular sites were injected simultaneously with 0.1 cc. of two of the three types of lepromin and observed for 48 hours. From a study of the early reactions produced, it was found that the three types were of approximately equal activity, the locally prepared crude lepromin giving at least as powerful a reaction as the purified varieties. As supplies of the latter were limited the same sample of crude lepromin was used in the majority of patients submitted to later tests.

For the purpose of these tests, patients were divided into six groups according to the type of macule they exhibited, as follows.

Group 1. Optimal allergic macules, well defined tuberculoid or

simple neural macules, exhibiting spontaneous resolution, nerve involvement usually present.

Group 2. Macules well defined, but exhibiting deficient resolution.

Group 3. Macules showing deficiency of resolution and also lack of definition, tending to spread and coalesce.

Group 4. Macules numerous and discrete, resolution defective, nerve involvement slight or lacking, tendency in the macules to coalesce, bacteriologically negative.

Group 5. Macules very numerous, coalescent, nerve involvement rare, no resolution, bacilli scanty.

Group 6. Lepromatous macules. Very numerous, definition poor, coalescent, nerve involvement rare, bacilli numerous and persistent.

In each group, cases with raised and flat types of macule were sought.

In carrying out the tests, 0.1 cc. of one or other type of lepromin was injected intradermally into the skin of the macule, near to an active edge, and another 0.1 cc. was injected into normal skin. For purposes of control, an extract of skin obtained by biopsy from a non-leprous individual was used, and prepared by the Rogers and Muir method in a manner identical with that used for lepromin. 0.1 cc. of this was injected into the macule and into the normal skin, simultaneously with the lepromin, in the first 70 patients tested. Although slight reaction to this extract were obtained in some patients, it was found that this logical control to the lepromin tests in no way impaired the specificity of the latter. Readings were made after 24 and 48 hours, and in some patients after 32 hours. It was found that in general the early reaction was most marked after 24 to 32 hours, and towards the end of the series, when working with out-patients, the 48 hour reading was abandoned.

No special attempt was made to test a large number of patients in group 1, as a positive result was to be expected in all patients in this group. The numbers tested in other groups vary widely, as some types of macule are seen much more commonly than others.

RESULTS.

TABLE I.

GROUP 1. Macules of optimal tuberculoid type.

(a) *Raised Macules.*

	No. tested.	Strongly pos.	Positive.	Doubtful.	Negative
Macules	23	13	7	3	—
Normal skin	23	5	7	10	1

(b) *Flat Macules.*

Very few macules of this type were tested and results are not regarded as significant.

GROUP 2. Macules deficient in spontaneous resolution, but well defined.

(a) *Raised Macules.*

	No. tested.	Strongly pos.	Positive.	Doubtful.	Negative
Macules	30	14	13	3	—
Normal skin	30	2	13	8	7

(b) *Flat Macules.*

	No. tested.	Strongly pos.	Positive.	Doubtful.	Negative
Macules	10	5	3	1	1
Normal skin	10	—	9	—	1

GROUP 3. Macules showing deficiency of resolution and also lack of definition, tending to spread and coalesce.

(a) *Raised Macules.*

	No. tested.	Strongly pos.	Positive.	Doubtful.	Negative
Macules	68	34	27	6	1
Normal skin	67	8	30	17	12

(b) *Flat Macules.*

	No. tested.	Strongly pos.	Positive.	Doubtful.	Negative
Macules	39	14	21	10	4
Normal skin	39	2	13	10	14

GROUP 4. Macules numerous but discreet, resolution defective, nerve involvement slight or lacking, tendency to coalesce, bacteriologically negative.

(a) *Raised Macules.*

	No. tested.	Strongly pos.	Positive.	Doubtful.	Negative
Macules	31	18	7	4	2
Normal skin	29	5	8	11	5

(b) *Flat Macules.*

	No. tested.	Strongly pos.	Positive.	Doubtful.	Negative
Macules	42	7	18	14	3
Normal skin	42	—	11	17	14

GROUP 5. Macules numerous, coalescent, nerve involvement rare, no resolution, bacilli persistent but scanty.

(a) *Raised Macules.*

	No. tested.	Strongly pos.	Positive.	Doubtful.	Negative
Macules	34	8	13	5	3
Normal skin	34	2	8	11	13

(b) *Flat Macules.*

	No. tested.	Strongly pos.	Positive.	Doubtful.	Negative
Macules	35	6	17	8	4
Normal skin	35	—	11	13	11

GROUP 6. Lepromatous macules. Very numerous, definition poor, lopromatous, bacilli numerous and persistent.

(a) *Raised Macules.*

	No. tested.	Strongly pos.	Positive.	Doubtful.	Negative
Macules	40	12	22	4	2
Normal skin	35	—	9	13	13

(b) *Flat Macules.*

	No. tested.	Strongly pos.	Positive.	Doubtful.	Negative
Macules	22	6	8	6	2
Normal skin	22	2	6	10	4

In order to simplify comparisons between one group and another, these results are given as percentages of the total in each group in the following tables.

TABLE II. Lepromin results in patients with raised macules.

(a) *Tests in Macules.*

Group.	Strongly positive. %	Positive. %	Doubtful. %	Negative %
1	57	30	13	nil
2	47	43	10	nil
3	50	40	9	1
4	58	23	13	6
5	24	53	14	9
6	30	55	10	5

(b) *Tests in normal skin.*

Group.	Strongly positive. %	Positive. %	Doubtful. %	Negative %
1	22	30	44	4
2	7	43	27	23
3	12	45	25	18
4	17	28	38	17
5	6	24	32	38
6	nil	26	37	37

TABLE III. Lepromin results in patients with flat macules.

(a) *Tests in Macules.*

Group.	Strongly positive. %	Positive. %	Doubtful. %	Negative %
1	—	—	—	—
2	50	30	10	10
3	29	43	20	8
4	17	43	33	7
5	17	49	23	11
6	27	37	27	9

(b) *Tests in normal skin.*

Group.	Strongly positive. %	Positive. %	Doubtful. %	Negative %
1	—	—	—	—
2	—	90	—	10
3	4	26	42	28
4	—	26	40	34
5	—	31	38	31
6	9	27	50	18

OBSERVATIONS.

1. These results demonstrate that hypersensitiveness to lepromin is not the monopoly of optimal tuberculoid macules, but may be found in macules of every type, including lepromatous macules.

2. The results of the test in macules are often in marked

contrast with those in normal skin, especially at the lepromatous end of the series. The test in normal skin shows a progressive decline in positivity towards the lepromatous group, a finding in line with most published results. In macules, however, this tendency is very much less, strikingly so in raised macules. It follows that in macular leprosy hypersensitivity to lepromin may be localised, and may be exhibited at the site of infection even though it is not a property of normal skin.

3. In view of this allergy, it is desirable that records of lepromin tests should specify whether these have been performed in normal skin or not. Although it is a simple matter to select normal skin when macules are localised, this is far from being the case at the lepromatous end of the series, where widespread coalescence of macules may mask their existence.

4. In the raised macule series, the percentage of positive results remains between 77-90% throughout the series. This means that hypersensitivity to lepromin is not an infallible guide to the clinical outcome, for lepromatous macules, destined in many cases to degenerate into diffuse leproma, still gave positive results.

5. Results in raised macules are compared with those in flat macules in Table IV, in which figures from all groups are added together and expressed as percentages of the total.

TABLE IV. Comparison of raised with flat macules.

	Strongly positive. %	Positive. %	Doubtful. %	Negative %
Raised macules	44	44	11	3
Flat macules	25	42	25	8

Results in flat macules are thus set at a lower level than in raised macules. Two factors may be responsible for this.

(a) Flat macules represent a milder response than raised macules, as histological studies of the optimal group indicate.

(b) Although throughout the series, efforts were made to select active cases, a proportion of flat macules were undoubtedly slightly raised macules in the process of resolution, and this additional factor may influence results.

6. It is necessary to notice that out of 385 macules tested, 22 were negative, and 64 gave a doubtful result. Of the 22 negative results, 8 were derived from the raised series, 14 from the flat series.

These observations accord with the characteristics of allergy in leprosy summarised in Part I, and it may be asserted with

confidence that whatever other factors are involved, allergy is implicated in the production of macules of all types. In the leprous macule we see the visible resultant of the action of two major opposing forces : on the one hand the living leprosy bacillus, and on the other the defence mechanism of the skin, consisting of (a) the basic monocyte response, and (b) allergic hypersensitiveness with its antibody production and specific cellular reaction. Both sides in this conflict are inconstant, and both are influenced by secondary factors, and the macule is thus not a static form of the disease, but is dynamic, changing with variations in the factors responsible for it.

The dynamic nature of macules is well illustrated by the changes in type of macule which a single patient may exhibit from time to time. Recurrence in an old minor tuberculoid lesion may take the form of a spreading flat macule. An initial macule may be succeeded by a crop of macules ranging from major tuberculoid to lepromatous in type. The clinical appearance thus reflects the patient's immunological state at the moment only, and if the current response is unable to obliterate the infection, active macules of another type may later follow local spread of bacillary metastasis.

The effectiveness of the allergic response is determined by its timing and persistence rather than by its intensity. An optimal major tuberculoid response, far outweighing the bacillary force ranged against it, is usually fully effective, but it is not rare to see patients with highly elevated succulent lesions, anaesthetic, but scarcely hypopigmented, their edge poorly defined, in which bacilli are numerous and persistent. Such lesions may be strongly positive to lepromin, far more so than the surrounding skin, and the clinical outcome remains uncertain. Here it is apparent that the intensity of the response is not the decisive factor. It is indeed probable that its intensity and its persistence tend to vary inversely. This and similar questions can only be clarified by the observation of the lepromin test in macules of various types throughout their history, and work of this nature is continuing.

My thanks are due to Mr. M. Smith, B.Sc. for technical assistance with lepromin tests, and to The Honourable Director of Medical Services, Nigeria, for permission to publish.

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DIASONE IN THE TREATMENT OF LEPROSY.

E. MUIR.

In 1944-45 I had an opportunity of testing the effect of diasone in the treatment of some 83 patients in Trinidad, B.W. Indies. Unfortunately on my leaving Trinidad in February, 1945, I had to discontinue the test, but a preliminary report was published. (Muir, 1944.) In this the opinion was expressed that without doubt diasone is of definite value in the treatment of leprosy especially in clearing up febrile and inflammatory conditions associated with lepra reaction. The question was raised as to whether diasone has a direct effect in destroying or preventing the growth of the leprosy bacillus, or whether improvement is attributable only to the destruction of accompanying pyogenic organisms which had complicated the majority of cases in the trials. To determine this a few patients in the early stage of the lepromatous type and not yet affected by septic complications, had been included. These had shown improvement but there had not been time to determine whether the treatment would lead to complete elimination of lepra bacilli.

The results obtained in the first trials were considered encouraging and, though it was still too soon to make any definite statement as to the extent to which this drug would be of use, there was reason to believe that a distinct step forward had been made in the treatment of leprosy.

After returning to England I had, through the kindness of the Department of Medicine, Abbott Laboratories, an opportunity of arranging for supplies of diasone to be sent for further trials to two suitable centres in India and one in West Africa, and also of making trials myself in twelve patients in this country. The

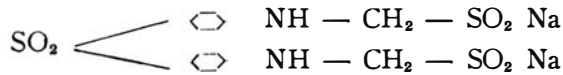
following brief report gives the details of treatment and the results so far obtained in these twelve patients, most of whom have now been taking diasone for over a year.

In the Trinidad trials the majority received the drug intravenously and some orally, but there was not time to determine which of these methods was preferable. In the present test the oral method has been used alone.

The few patients available for trial in this country did not allow of selection of cases. Of the twelve, ten were fairly advanced lepromatous cases, and two may be described as intermediate, although at the commencement of treatment their bacteriological examinations gave strongly positive results.

METHOD OF ADMINISTRATION.

Diasone is described as the di-sodium formaldehyde sulphoxylate derivative of diaminodiphenyl sulphone.



It is supplied as a white powder and is usually made up in $\frac{1}{3}$ gram capsules. Previous clinical observations in tuberculosis have shown that in that disease the most suitable dose is 1 gram per day, although patients have tolerated daily doses of 5-7 grams for periods up to a maximum of 6 weeks. Two grams a day has been found to cause anaemia unless iron, along with liver or yeast, is administered.

Relying on the previous experience referred to, we adopted the plan of giving one capsule on alternate days three times a week, say on Mondays, Wednesdays and Fridays and, provided there are no contra-indications, increased the dose on each of these three days by one capsule every week until 6 capsules three times a week was reached in the sixth week. After this, provided the patient was doing well and there was no reason to the contrary, diasone was given in addition on Tuesdays, Thursdays and Saturdays, again beginning with one capsule on each day and increasing by one capsule each day up to six.

Thus, as is shown in the table, the patient reached the average dose of six capsules (approximately 2 grammes) a day six days a week. This is considered to be the maximum for a patient of 140 lbs. weight, but it may be increased or diminished according to the weight. After the maximum dose is reached each three weeks' period of treatment is followed by a week's rest without diasone.

DOSAGE TABLE.

Week.	Number of Capsules.					
	Mon.	*Tues.*	*Wed.*	*Thurs.*	*Fri.*	*Sat.*
1	1		1		1	
2	2		2		2	
3	3		3		3	
4	4		4		4	
5	5		5		5	
6	6		6		6	
7	6	1	6	1	6	1
8	6	2	6	2	6	2
9	6	3	6	3	6	3
10	6	4	6	4	6	4
11	6	5	6	5	6	5
12	6	6	6	6	6	6
13	0	0	0	0	0	0
14	6	6	6	6	6	6
15	6	6	6	6	6	6
16	6	6	6	6	6	6
17	0	0	0	0	0	0

CONTRA-INDICATIONS.

The danger signals or reasons for diminishing or temporarily discontinuing diasone treatment are lepra reaction and anaemia.

1. *Lepra reaction.* This shows itself by a rise of temperature, by the flaring up of existing clinical lesions or the appearance of new lesions. In the beginning of treatment diasone often has the effect of alleviating this condition where it already exists, and causes healing of ulcers, clearing up inflammatory eye and nose complications.

On the other hand, after the treatment has been begun a dose, however small, which for the moment is excessive, may provoke reaction, and this is an indication for diminishing or temporarily stopping diasone treatment until the reaction has subsided. Gradually the patient becomes able to tolerate larger doses and signs of reaction become less marked until they disappear entirely.

2. *Anaemia.* In many advancing cases of the lepromatous type the patient suffers from anaemia, especially in the tropics. Before beginning treatment it is well to make a thorough blood examination, with special attention to the haemoglobin percentage. If this be below 75 per cent the patient should be given full doses of iron for at least a week before diasone treatment begins, and this should be continued along with the diasone till the percentage rises to 80 per cent or more.

Like other sulphone and sulphonamide drugs diasone has a tendency at first to cause or increase anaemia, and it is well to

make haemoglobin examinations once a week or fortnight during the early stages of the treatment. If the percentage in spite of iron continues to fall or remains low, then diasone should be stopped or the dose diminished temporarily and iron pushed. Sometimes also liver extract is of marked value.

In most patients in whom there is an initial tendency towards anaemia, this gradually diminishes and, as the general condition improves the haemoglobin percentage rises and remains at a high level and larger doses of diasone are tolerated.

3. Other complications to be watched for are renal and cardiac disease, but in none of the cases treated have these complications given any trouble.

TOLERANCE.

Apparently the body gradually acquires tolerance to diasone as, once the maximum dose mentioned has been reached, it is generally possible to continue indefinitely, giving 12 grammes a week for three weeks a month, without further occurrence of the two adverse signs mentioned above. Instead of flaring up, as the lesions are apt to do at the beginning of treatment, they gradually tend to flatten out and disappear and the haemoglobin percentage, which often inclines to be low in the lepromatous type of leprosy and to become lower at the beginning of treatment, may reach a higher level than the original level once the treatment is well under way. Once this stage has been reached it is possible to continue treatment for an indefinite period with a far less degree of supervision.

There are probably two factors which account for this tolerance. In the literature supplied by Messrs. Abbott Laboratories it is mentioned that when diasone is administered over a period of time the blood levels drop rapidly from what they are initially. "At a dosage level of 1 gram per day, the blood concentration ranges usually between 1.5 and 2 mg. per 100 cc. The blood concentration does not increase in proportion to an increased oral dose. A 100% increase in the daily oral dose will usually produce only a 10% to 20% increase in the diasone blood level. The diasone blood level begins to drop off in the majority of cases after a period of six to eight weeks therapy and continues to drop as the period of therapy extends, until there may be as little as 0.5 mg. or less per 100 cc. of blood." This would explain to a large extent the absence of anaemia and of reactionary signs after the initial period of treatment.

The other factor which might be expected to affect the latter if not the former of these complications is the improvement

of general health, the better appetite and ability to take more exercise which commonly follow the initial period of treatment.

It is not claimed that the method of dosage used in this trial is the safest, most economical and most effective. The fact that the blood level does not increase proportionately when the daily dose is increased above 1 gram, and that during six or eight weeks' treatment the blood level gradually falls till it is only a third or a quarter of the previous level, suggest that there might be an advantage in lengthening the periods both of administration and of rest. If the fall in blood level is due to lowering of the threshold of renal excretion, as suggested by the experimental work of Smith, Emmart and Stohlman (1943), it is important to find out what period of non-administration is necessary to restore the original threshold level. In three of our patients slight reactions followed the resumption of treatment after the period of rest, suggesting that a higher blood level had been reached resulting in this reaction. Careful experiments are called for to work out the safest and most effective dosage.

The following are reports of the twelve cases treated :—

Case 1. An L 3 case. Had been on hydnocarpus injections for several years. Both eyes were destroyed by leprosy. Diasone was begun on 20.8.45 and given three times a week, the first week 1 capsule to the dose, second week 2. After this it had to be stopped from 2nd to 12th September as there was a febrile reaction and nodules were coming out. On the 17th of September the dosage was renewed, 2 capsules being given three times a week for one week, then 3 capsules three times a week for three weeks. The dosage was then gradually raised to 6 capsules three times a week. From 28.3.46 dosage was raised to 6 capsules six days a week for three weeks, followed by one week's rest. This, however, had to be reduced because of febrile attacks. With 6 capsules three times a week and 1 or 2 on the alternate days, the temperature remains normal, but it should soon be possible to reach the maximum amounts. Since the reaction referred to there has been no further flare up of lesions but there is a slight reaction when treatment is resumed after a week's rest. The nodules have flattened out and the skin has become markedly thin and wrinkled. The patient is feeling considerably better. Bacterioscopy shows reduction of bacilli in the skin. In the nose the bacilli appear to be broken down and and very granular.

Case 2. An L 2-3 case. Had been on hydnocarpus treatment for several years. On this he had improved but had from time to time suffered reactions. He began diasone on 27.10.45 with 1 capsule three times a week. The dose was gradually increased up to 6 capsules three times a week. On 28.3.46 the dosage was raised to 6 capsules six times a week for three weeks, followed by one week's rest. There is now considerable thinning of the skin. For a time very small nodules appeared and disappeared within a day or two, but these have now become less. The patient's general health has improved. His left eye, which was considerably involved, has almost entirely cleared up, leaving an irregular pupil but with considerable reaction to light and 6/18 vision. The right eye which had begun to be involved has become normal, with regular fully reacting pupil and 6/6 vision. Bacterioscopy shows now only a few scattered bacilli in the skin; the nose shows large masses of bacilli but these are very granular and broken down.

Case 3. This patient, 7 years old, was first seen in the spring of 1945. There was considerable swelling of both ears and of the face,

and ring-shaped asymetrical lesions of the buttocks and trunk. Bacilli were present in biopsy smears from the ear and ring patches in considerable numbers. There was some doubt in prognosis as the conditions resembled in certain respects both types of leprosy, and he could therefore be considered an indeterminate case. The general health was bad and the patient anaemic. He was put on iron, and with this and careful nursing his general health improved. Diasone was begun on 9.8.45 one capsule being given three times a week for two weeks, then 2 capsules three times a week for four weeks, and then a permanent dosage of 3 capsules three times a week was introduced. On 15.9.45 very scanty bacilli were found. The thickening of the ears disappeared rapidly and the patches began to grow fainter. The patches were painted with trichloracetic acid and intradermal injections of moogrol given. On 16.2.46 smears from the ear and buttock were negative, as has been the case on subsequent examinations up to August, 1946. The patches have now almost entirely disappeared and the patient is in robust health. To what extent this improvement is due to better general health and natural causes, and how much is due to diasone, it is difficult to judge. Unfortunately there was not an opportunity of doing the lepromin test before treatment. When it was done recently it was found to be moderately positive.

Case 4. An L 3 case of long duration. Blind. On 27.10.45 he was given 200,000 units of penicillin. This was followed by a severe reaction and painful inflammation of the eyes and breaking down of ulcers. Within three weeks the ulcers had healed up again and the patient was feeling much better. He began diasone on 19.11.45 and his condition has continued to improve. Formerly he had repeated breaking down of the skin to form ulcers, and an inflammatory condition of the throat. These have now disappeared. He is taking 12 grammes of diasone weekly without ill effects. The bacteriological examination shows now only 8 bacilli in 100 fields.

Case 5. An L 3 case of long duration. Blind. He had been on chaulmoogra treatment for many years. He began diasone on 20.8.45, the thrice weekly dosage being increased every week from 1 up to 6 capsules. On 28.3.46 the administration of diasone was increased from three days a week to six. At first there was the appearing and fading of nodules. He soon began to feel much better than he had before, and there is now a distinct flattening of the raised skin lesions, many of which have been reduced to scars. Very slight reactions were noticed when treatment was resumed after a week's rest. Bacterioscopy shows only 5 bacilli in 14 fields in the skin and a few small clumps in the nose, a very considerable improvement from previous examinations.

Case 6. A bad L 3 case also with tuberculosis of the spine. Treatment with diasone in this case has had to be interrupted frequently because of the weakness of the patient and anaemia. She was given iron daily and anahaemin once a fortnight. Diasone was gradually increased to six capsules three times a week, and then to 6, 3, 6, 3, 6, 3. This patient had been on chaulmoogra for many years, but had got gradually worse. A remarkable thing is that after 9 months of diasone her lepromin test gave a double positive result one month after injecting 0.2 of Dharmendra's antigen. The test was done on two sites and both reacted. The nodule formed on the site of an apparently healed lesion, liquified and discharged. This patient is now remarkably well. At the beginning of treatment she had for long been bedridden, but is now able to walk actively about.

Case 7. An L 2 case. Diffuse nodules of the hands. Began diasone on 15.10.45, the dosage being gradually raised to 6 capsules three times a week, and on 28.3.46 raised to 6 capsules six days a week. The patient also has high blood pressure. Thick lepromatous patches and nodules of hands and knees have disappeared, or left scars. The eyes which were seriously involved, have become quiescent. The general health has improved. This patient also shows slight signs of reaction when treatment is resumed after a week's rest.

Case 8. This patient has been suffering for many years and was a severe L 3 case, with considerable ulceration of various parts of the body,

especially the fingers. Before he began diasone he was very weak and could only walk a short distance. Diasone was begun on 10.8.45 with 3 capsules six days a week, increasing by 1 capsule a day up to a maximum of 7 capsules. On 31.3.46 as there were signs of reaction, the administration was changed from 6 to 3 days a week. At first there were shortness of breath, digestive disturbances and other symptoms such as dizziness, frequent micturation and, on one occasion, palpitations. The patient was put on iron beginning with small doses and gradually rising to 30 grains of ferrous carbonate daily. Diasone treatment was interrupted on the 6th of September owing to marked dizziness, on the 20th of October due to indigestion and anaemia, and on January 5th, 1946, owing to indigestion and palpitations. The last of these, however, may have been due to an attack of influenza. There was three weeks' interruption of treatment in all. The doctor now in charge of the case reports that "there is no doubt that the results of diasone have been most spectacular. The nodules have been much absorbed. The general effect on the psychological side has been amazing, as he does not mind going out now nearly as much as he did. I kept him on a course of iron the whole time. It seems to keep his haemoglobin up to 80%." In August, 1945, the patient could walk only about 1½ miles a day. From January, 1946 he has gradually increased the distance and can now walk four miles a day. His eyesight has improved and there is no tendency to the recurrence of ulcers of the skin. The finger nails have improved, also the tendency to scaling, and the whole condition of the skin has improved.

Case 9. I have not myself seen this patient, but have treated him through correspondence with his own doctor. There were abundant bacilli in the nasal secretion and tiny ulcers on the hands, scalp and legs. Diasone treatment was begun on 14.1.46, the dose gradually rising to 5 capsules three times a week. The doctor reports that "at the outset I found abundant bacilli in the nasal secretion, in smears from tiny ulcers of the hands, scalp and legs, and in apparently normal skin of the lobe of the ear. Smears from nose and scalp ulcers were still positive on 12.2.46 and from the ulcer on the hand on 18.2.46, but yesterday, 15.4.46, all the ulcerations had healed, there was no nasal discharge, and from 2.4.46 onwards nasal smears have been negative for M. leprae. He looks and feels very much better, but he has parasthesia of the fingers still, though even this symptom is less than at the beginning of treatment. I found his haemoglobin to be fully 90% three weeks ago. My impression is that diasone has done quite as well as moogrol and, as injection had become a real difficulty, oral treatment has been a great boon and has given him encouragement which it would be hard to over estimate." Not having seen this case I am unable to determine definitely the type of disease, and consequently to what extent the improvement might have been due to diasone and to what extent to natural causes.

Case 10. An L 3 case of long duration. He began diasone in the end of January, 1946. Has been on 6 capsules weekly for some months and is now gradually being raised to 12 grammes a week. Hb 90%. This patient has very definitely improved. His eyes had been badly damaged by leprosy but under diasone became quiescent. It was thus possible recently to do an iridectomy which has considerably improved vision. Cutaneous nodules have flattened out and the skin infiltration became much less.

Case 11. An L 3 case of two years' known duration. Diffuse infiltration with several nodules and raised plaques. On diasone since June, 1946. It is still too soon yet to report on this case, but the doctor in whose charge is the treatment, reports that nodules and pigmentation have disappeared and the general condition of the patient has improved.

Case 12. This patient, an L 2-3 case, suffering from leprosy for over 13 years, was admitted to hospital in a bad condition suffering from cystitis and a purulent eye condition. Has been on diasone since May, 1946 and is now taking 12 grammes per week. The septic conditions have cleared up under appropriate treatment. As regards leprosy there is definite impovement, but to what extent this is due to diasone, and to what extent to the general betterment of health, it is difficult yet to say.

DISCUSSION.

In all patients without exception there has been improvement, and in some marked improvement. Case No. 3 became bacteriologically negative and all other active signs have now been absent for some months, but to what extent this is due to diasone it is impossible to say.

One of the most delicate tests of improvement is the eye condition. In cases 2, 6, 7 and 10 gradual eye deterioration, which would have been expected in the usual course to lead soon to complete blindness, has been arrested and vision to a certain extent restored.

Cases 1, 2, 4, 5, 6, 8, and 10 had all been on chaulmoogra treatment for years but, in spite of this, were gradually becoming worse. Under diasone, either from the beginning or after a few weeks' or months' treatment, they have all made steady and definite improvement. One striking sign of improvement is the gradual cessation of febrile attacks and crops of nodules from which they had suffered for years. Also the steady improvement and maintenance of general health. What the final result in these cases will be it is still too soon to say.

In the former report referred to in the beginning of this paper the question was raised as to whether diasone has a direct effect in destroying or preventing the growth of the leprosy bacillus, or whether improvement is attributable only to the destruction of accompanying pyogenic organisms which had complicated the majority of cases in the earlier trials. In the present cases septic complications have been practically absent, and there is thus clearer evidence that diasone has the power of clearing up, at least to a certain extent, uncomplicated lepromatous lesions in a great majority of cases. How far this process will continue and how it is brought about it is still too early to form any opinion.

During more than 27 years of experience of leprosy treatment and the trial of many drugs, the author has not seen any remedy for definite lepromatous cases of leprosy which has given such uniformly favourable results.

Whatever effective treatment is found for the lepromatous type of leprosy it is likely to be prolonged except when it is begun in the early stages of the disease. In highly endemic areas, such as those in India, China and Africa, there are large numbers of cases to be treated, and skilled staff is generally very limited in number. There are therefore three requirements to be met by any drug that is to be really effective :—

(1) It must be of sufficiently low toxity so that, at least after

the early stages of treatment, it can be safely administered without elaborate tests requiring considerable time and skill, and can be tolerated over a period sufficiently long.

(2) It should be easy to administer and capable of being given by mouth.

(3) It must be able to bring about steady improvement in the average case until the disease entirely disappears, and to prevent relapse.

(4) It should be easy to manufacture and therefore capable of being produced in sufficient quantity and at a low enough price, having reference to the poverty of the patients and of their countries.

Diasone appears to meet the first two and, at least to a certain extent, the third of these requirements. The majority of patients treated have been turned from gradually deteriorating into gradually improving cases, though it is still too soon to say more than this. Similar favourable results have been obtained with other drugs of the sulphone group, and there is reasonable hope that from this beginning advance will be made to drugs even more effective in the treatment of leprosy.

Regarding the fourth requirement, it is too soon yet to say if diasone can be produced in sufficient quantity and at a price low enough to make it available for the thousands of indigent patients in such countries as those mentioned. The initial expense in large scale manufacture is bound to be great, and it is difficult for private firms of manufacturing chemists to meet this expenditure when there is no assurance that their product may not be superseded by something yet more effective after a short time.

SUMMARY.

1. Following on a test of diasone in the treatment of 83 patients in the West Indies, which was previously reported on, the author made a further test in twelve patients.

2. The method of administration is described; the dosage is carefully regulated till a maximum of 12 grammes a week for 3 weeks in the month is reached.

3. Details of the treatment and results in each case are given.

4. Beneficial results were obtained in all cases, though it is still too early to estimate the full and final results.

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PROMIN THERAPY.

L. H. WHARTON.

This is a report on the results of treatment of seven cases for one year.

It was not until August 1945 that we were able to obtain from the U.S.A. a small supply of promin for intravenous injection. We selected seven advanced lepromatous cases (L_3 type) all young adults, who were rapidly going downhill in spite of many years of the orthodox Chaulmoogra treatment. These patients belonged to the 20-30 year age group, 3 were men, and 4 women. All the patients were suffering from serious complications of the disease, deep chronic ulcers of the legs, superficial ulcerating nodules of the hands and face, ulcers of the nasal septum, oedema of the face and legs. Two patients were practically blind, one suffering from keratitis, and one from iridocyclitis. Two had conjunctivitis and three rhinitis. Physically these patients were weak, and were all mentally dejected.

Before treatment complete blood counts and urinalysis were done, and these were repeated every two weeks throughout the year. The patients were all eager to take the treatment.

The course consisted of 2 grammes intravenously daily for the first six days, and then one day's rest. The dose was gradually increased by 1 gramme weekly until a maximum of 5 grammes was reached. It was then continued at 5 grammes daily throughout the year. At the end of every six weeks of treatment one week's rest was given.

At the end of the first month, there was a marked improvement in the physique and mental outlook of the patients. Their appetites were markedly improved, and they began to take an interest in themselves and their surroundings again. The ulcers were all clean. At the end of three months the chronic ulcers were showing rapid signs of healing, the oedema of the face and legs had subsided, and the patients were gradually assuming their normal appearance. The eye conditions had not progressed and seemed to be arrested. Rhinitis had subsided, and nasal ulcers were healing. At the end of six months the chronic ulcers had healed completely, this was most remarkable as these ulcers had resisted all forms of treatment for many years. The patients were all free from ulcer dressings, and were very pleased about this. Nasal ulcers were also healed, and nodules were flattening out. No new nodules had appeared. In the eye cases although there was no marked improvement in vision, the condition had not become worse.

So great was the improvement at the end of six months that the other lepromatous cases demanded the drug. With difficulty we were able to obtain a larger supply and treatment was started on 70 patients.

In the second six months treatment of the orginal seven patients they continued to improve, and none of these patients had any relapses, or showed any symptoms of drug toxication.

A careful watch was kept on the blood count and urinalysis throughout the course. If the red blood count fell below 4 million a simple iron mixture was given. If it fell to 3½ million liver extract was given, and if it fell to 3 million treatment was discontinued and liver and iron given until a count of 3½ million was obtained before continuing treatment.

None of the patients developed any kidney complications. The patients were allowed to perform their normal duties throughout the course. It is proposed to continue the treatment for another year.

BACTERIOLOGICAL RESULTS.

Nasal and skin smears of the first seven cases were all M/1 at the commencement. (The enumerator M denoting more than 10 bacilli, and the denominator 1 denoting the number of fields.)

After a year all these patients were still positive.

Bacillary Counts.

Before Promin.	*Skin.*	*Nose.*	*After Promin.*	*Skin.*	*Nose.*
1st Case	M/1	M/1	1st Case	18/10	M/1
2nd „	„	„	2nd „	26/10	„
3rd „	„	„	3rd „	16/10	„
4th „	„	„	4th „	22/10	„
5th „	„	„	5th „	19/10	„
6th „	„	„	6th „	15/10	35/10
7th „	„	„	7th „	13/10	M/1

While the above bacillary counts show a marked diminution in skin smears, there has been practically no difference in nasal smears.

HISTOLOGICAL CHANGES.

Biopsies were taken before and after treatment :

Before promin :— Portion of skin examined showed typical lepromatous granulomatous tissue with many leprous cells packed with bacilli. There was very little fibrous connective tissue.

After promin :— Portion of skin examined showed very little lepromatous granulomatous tissue with much fibrous connective tissue. There were very few leprous cells with few bacilli, and relatively less infiltration with mononuclear cells.

DISCUSSION.

One theory has been put forward that while promin is not bacteriocidal to Mycobacterium leprae it probably acts on complicating pyogenic micro-organisms. As against this we have found that four of the seven patients developed several attacks of lepra reactions during the course.

The seventy patients who have had six months' treatment with the drug have all shown remarkable improvement, especially as regards the healing of chronic ulcers.

CONCLUSION.

We are of opinion that the beneficial results obtained by the use of promin are due to the fact that the drug acts on the lepromatous tissue which is destroyed, with the formation of fibrous connective tissue. In the process leprous cells are destroyed, and the reduction in bacilli is due to their being unable to multiply.

We consider promin a safe drug to give over long periods. It is definitely a most useful drug in the treatment of leprosy.

I wish to express my sincere thanks to Dr. B. G. Nehaul, Government Bacteriologist, for his report on the histological sections, and for his valuable assistance in trying out new staining techniques.

REVIEWS.

Promizole Treatment of Leprosy, by Faget, G. H., Pogge, R. C. and Johanson, F. A., *U.S.A. P.H. Rep.* 61, 957, (1946).

Promizole is the trade name for 2, 4'-diamino-5-thiasolylphenyl sulfone. Seven out of an original group of eleven patients were under treatment with promizole at the U.S.A. National Leprosarium for a year. The following conclusion was arrived at:

"No claim is made in regard to the ultimate value of promizole given orally in doses of 6 gm. daily in the treatment of leprosy. Attention is called to the fact that promizole is well tolerated by patients with leprosy, and that clinical improvement occasionally can be demonstrated more quickly with promizole than with similar sulfones, such as promin and diasone. It is felt that the therapeutic results thus far obtained are sufficiently encouraging to warrant further clinical study, which will be necessary before a final evaluation of promizole in the treatment of leprosy can be given."

A plate illustrates the rapid changes in lepromatous lesions of two cases after only 3 months.

Present Status of Diasone in the Treatment of Leprosy, by Faget, G. H., Pogge, R. C. and Johansen, F. A. *U.S.A. P.H. Rep.* **61**, 960, (1946).

Out of 104 patients selected, 63.5 per cent had received treatment for six months or more at the time of the communication. The authors' report as follows :—

"It would appear from our clinical observations that diasone has an action similar to that of promin, which has been reported in considerable detail. Treatment with diasone has the advantage that the drug is tolerated in doses up to 1.0 gm. daily for long periods of time. The number of patients in whom treatment was discontinued because of anaemia is low, because many of the patients receive liver or iron products with the diasone. The number in whom treatment was discontinued because of hematuria is limited to four patients, who were started with doses of 1.0 gm. daily early in the study. At the present time diasone is administered in doses of 0.33 gm. daily for the first 2 weeks, and then gradually increased to 1.0 gm. Since the adoption of this policy there have been no further cases of hematuria."

The progress of four of the cases is illustrated with very striking photographs.

Leprosy in Spain. A booklet recently issued by Dr. Felix Contreras Duenas deals with this subject. After discussing the nature of leprosy and its spread, and recording the history of the disease in Spain, he quotes the various authorities on the subject regarding the present incidence of the disease. In Andalusia there are said to be 2,000 cases, in the Levantine Provinces 1,300, and 600 in Galicia, or about 4,000 altogether, but he considers that this is an under-estimate and that the total number may be 8,000. There are also said to be 650 in the Canary Isles and 8,000 in Spanish Guinea. Of those in Spain proper, there are at present 210 in the leprosy hospital at Fontilles, in Alicante, and 178 divided among five smaller institutions. The author considers that for the 8.000 cases in Spain proper provision should be made for the institutional segregation of 2,000, and dispensary treatment for 5,000 closed cases, while 1,000 would be treated privately at home.

The Control of Leprosy among the Azande, Anglo-Egyptian Sudan. (1946), Bloss, J. E. F., *Trans. Roy. Soc. Trop. Med. and Hyg.* **39**, 423.

The writer reviews, after twelve years of anti-leprosy measures, the control of leprosy attained among the Azande people of the Anglo-Egyptian Sudan.

In 1929, while making a sleeping sickness investigation, a

survey of leprosy was also carried out in the Zande country, and 6,400 cases were found among a population of approximately 180,000, making about 3.5 per cent. Of these 5,500 cases were at first segregated in two leprosy settlements. It is remarkable that only 20 per cent of these were of the neural type, whereas in most highly endemic areas 80 per cent of neural cases would be more likely. Twenty per cent were under twenty. The leprosy settlements were placed with chiefs, with a part-time doctor in charge, but many of the patients deserted to their homes and only the worst cases remained. In 1935 there were 204 advanced cases segregated, 1,021 under observation and treatment in the settlement, 809 outside cases that had never been in the settlement, and 1,464 discharged cases living inside or outside the settlement. In 1942, 60 per cent of patients in the Li Rangu Settlement were neural cases, 54 per cent being N1 cases. In that year the total incidence is calculated as being very similar to that 12 years before, but the age incidence shows less than 12 per cent are under 20 years of age, and new cases among children are comparatively rare. The writer gathers from these observations that leprosy is now under control and on the decrease. He considers that the low protein content of the diet and the absence of meat due to the tsetse fly, is the chief cause of leprosy. [In this he differs from most recent writers on the subject, who tend to ascribe a secondary, though still important, role to diet.] He hopes that with economic development, the control of other endemic diseases, and improved education leprosy will tend to die out. While the large form of leprosy settlement is still necessary, it should be changed to smaller " chiefs " settlements as soon as education has had time to produce intelligent and full support from chiefs and people. This it is hoped " will come in the fullness of time, but to force it at the wrong time would cause chaos." [This policy may be necessary where sufficient suitable staff is not available. It is in very marked contrast to the method adopted, say, in the Owerri Province of Nigeria, where a similarly high incidence of leprosy is being used as a means to educate the community, improve the standard of living, and win the co-operation of chiefs and people, incidentally bringing leprosy under control.]